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(54) Title: NOVEL G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The present invention provides a gene encoding a G protein-coupled receptor termed nGPCR-x; constructs and recombinant host cells incorporating the genes, the nGPCR-x polypeptides encoded by the gene, antibodies to the nGPCR-x polypeptides, and methods of making and using all of the foregoing.

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NOVEL G PROTEIN-COUPLED RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority of Application Serial No. 60/187,584, filed March 8, 2000; Serial No. 60/187,707, filed March 8, 2000; Serial No. 60/187,708, filed March 8, 2000; Serial No. 60/188,290, filed March 8, 2000; Serial No. 60/188,292, filed March 8, 2000; Serial No. 60/187,827, filed March 8, 2000; Serial No. 60/188,293, filed March 8, 2000; Serial No. 60/187,639, filed March 8, 2000; Serial No. 60/187,583, filed March 8, 2000; Serial No. 60/187,709, filed March 8, 2000; Serial No. 60/187,637, filed March 8, 2000; Serial No. 60/187,640, filed March 8, 2000, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates generally to the fields of genetics and cellular and molecular biology. More particularly, the invention relates to novel G protein coupled receptors, to polynucleotides that encode such novel receptors, to reagents such as antibodies, probes, primers and kits comprising such antibodies, probes, primers related to the same, and to methods which use the novel G protein coupled receptors, polynucleotides or reagents.

BACKGROUND OF THE INVENTION

The G protein-coupled receptors (GPCRs) form a vast superfamily of cell surface receptors which are characterized by an amino-terminal extracellular domain, a carboxyl-terminal intracellular domain, and a serpentine structure that passes through the cell membrane seven times. Hence, such receptors are sometimes also referred to as seven transmembrane (7TM) receptors. These seven transmembrane domains define three extracellular loops and three intracellular loops, in addition to the amino- and carboxy-terminal domains. The extracellular portions of the receptor have a role in recognizing and binding one or more extracellular binding partners (*e.g.*, ligands), whereas the

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intracellular portions have a role in recognizing and communicating with downstream molecules in the signal transduction cascade.

The G protein-coupled receptors bind a variety of ligands including calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and even photons, and are important in the normal (and sometimes the aberrant) function of many cell types. [See generally Strosberg, *Eur. J. Biochem.* 196:1-10 (1991) and Bohm *et al., Biochem J.* 322:1-18 (1997).] When a specific ligand binds to its corresponding receptor, the ligand typically stimulates the receptor to activate a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) that is coupled to the intracellular portion of the receptor. The G protein in turn transmits a signal to an effector molecule within the cell, by either stimulating or inhibiting the activity of that effector molecule. These effector molecules include adenylate cyclase, phospholipases and ion channels. Adenylate cyclase and phospholipases are enzymes that are involved in the production of the second messenger molecules cAMP, inositol triphosphate and diacyglycerol. It is through this sequence of events that an extracellular ligand stimuli exerts intracellular changes through a G protein-coupled receptor. Each such receptor has its own characteristic primary structure, expression pattern, ligand-binding profile, and intracellular effector system.

Because of the vital role of G protein-coupled receptors in the communication between cells and their environment, such receptors are attractive targets for therapeutic intervention, for example by activating or antagonizing such receptors. For receptors having a known ligand, the identification of agonists or antagonists may be sought specifically to enhance or inhibit the action of the ligand. Some G protein-coupled receptors have roles in disease pathogenesis (*e.g.*, certain chemokine receptors that act as HIV co-receptors may have a role in AIDS pathogenesis), and are attractive targets for therapeutic intervention even in the absence of knowledge of the natural ligand of the receptor. Other receptors are attractive targets for therapeutic intervention by virtue of their expression pattern in tissues or cell types that are themselves attractive targets for therapeutic intervention. Examples of this latter category of receptors include receptors expressed in immune cells, which can be targeted to either inhibit autoimmune responses or to enhance immune responses to fight pathogens or cancer; and receptors expressed in

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the brain or other neural organs and tissues, which are likely targets in the treatment of mental disorder, depression, bipolar disease, or other neurological disorders. This latter category of receptor is also useful as a marker for identifying and/or purifying (*e.g.*, via fluorescence-activated cell sorting) cellular subtypes that express the receptor. Unfortunately, only a limited number of G protein receptors from the central nervous system (CNS) are known. Thus, a need exists for G protein-coupled receptors that have been identified and show promise as targets for therapeutic intervention in a variety of animals, including humans.

SUMMARY OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or a fragment thereof. The nucleic acid molecule encodes at least a portion of nGPCR-x. In some embodiments, the nucleic acid molecule comprises a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, and fragments thereof.

According to some embodiments, the present invention provides vectors which comprise the nucleic acid molecule of the invention. In some embodiments, the vector is an expression vector.

According to some embodiments, the present invention provides host cells which comprise the vectors of the invention. In some embodiments, the host cells comprise expression vectors.

The present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, said portion comprising at least 10 nucleotides.

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The present invention provides a method of producing a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or a homolog or fragment thereof. The method comprising the steps of introducing a recombinant expression vector that includes a nucleotide sequence that encodes the polypeptide into a compatible host cell, growing the host cell under conditions for expression of the polypeptide and recovering the polypeptide.

The present invention provides an isolated antibody which binds to an epitope on a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or a homolog or fragment thereof.

The present invention provides an method of inducing an immune response in a mammal against a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or a homolog or fragment thereof. The method comprises administering to a mammal an amount of the polypeptide sufficient to induce said immune response.

The present invention provides a method for identifying a compound which binds nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether the compound binds nGPCR-x.

The present invention provides a method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x. The method comprises the steps of contacting said nucleic acid molecule encoding nGPCR-x with a compound and determining whether said compound binds said nucleic acid molecule.

The present invention provides a method for identifying a compound which modulates the activity of nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether nGPCR-x activity has been modulated.

The present invention provides a method of identifying an animal homolog of nGPCR-x. The method comprises the steps screening a nucleic acid database of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or portion thereof.

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The present invention provides a method of identifying an animal homolog of nGPCR-x. The methods comprises the steps screening a nucleic acid library of the animal with a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or a portion thereof; and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or a portion thereof.

Another aspect of the present invention relates to methods of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor. The methods comprise the steps of assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain. The nGPCR-x comprise an amino acid sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and allelic variants thereof. A diagnosis of the disorder or predisposition is made from the presence or absence of the mutation. The presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

The present invention further relates to methods of screening for a nGPCR-x hereditary mental disorder genotype in a human patient. The methods comprise the steps of providing a biological sample comprising nucleic acid from the patient, in which the nucleic acid includes sequences corresponding to alleles of nGPCR-x. The presence of one or more mutations in the nGPCR-x allele is indicative of a hereditary mental disorder genotype.

The present invention provides kits for screening a human subject to diagnose mental disorder or a genetic predisposition therefor. The kits include an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene. The oligonucleotide comprises 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution. The kit also includes a media packaged with the oligonucleotide. The media contains information for

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identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

The present invention further relates to methods of identifying nGPCR-x allelic variants that correlates with mental disorders. The methods comprise the steps of providing biological samples that comprise nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny, and detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain. The nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and allelic variants thereof. The nucleic acid includes sequences corresponding to the gene or genes encoding nGPCR-x. The one or more mutations detected indicate an allelic variant that correlates with a mental disorder.

The present invention further relates to purified polynucleotides comprising nucleotide sequences encoding alleles of nGPCR-x from a human with mental disorder. The polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS. The polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240 by at least one residue.

The present invention also provides methods for identifying a modulator of biological activity of nGPCR-x comprising the steps of contacting a cell that expresses nGPCR-x in the presence and in the absence of a putative modulator compound and measuring nGPCR-x biological activity in the cell. The decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

The present invention further provides methods to identify compounds useful for the treatment of mental disorders. The methods comprise the steps of contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x. The

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binding between nGPCR-x and the compound suspected of binding nGPCR-x is detected. Compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of mental disorder. Compounds identified as binding nGPCR-x may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

The present invention further provides methods for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x. The methods comprise the steps of contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound and detecting binding between the binding partner and nGPCR-x. Decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a related disease or disorder. Compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

Another aspect of the present invention relates to methods of purifying a G protein from a sample containing a G protein. The methods comprise the steps of contacting the sample with an nGPCR-x for a time sufficient to allow the G protein to form a complex with the nGPCR-x; isolating the complex from remaining components of the sample; maintaining the complex under conditions which result in dissociation of the G protein from the nGPCR-x; and isolating said G protein from the nGPCR-x.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

Various definitions are made throughout this document. Most words have the meaning that would be attributed to those words by one skilled in the art. Words specifically defined either below or elsewhere in this document have the meaning provided in the context of the present invention as a whole and as are typically understood by those skilled in the art.

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"Synthesized" as used herein and understood in the art, refers to polynucleotides produced by purely chemical, as opposed to enzymatic, methods. "Wholly" synthesized DNA sequences are therefore produced entirely by chemical means, and "partially" synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

By the term "region" is meant a physically contiguous portion of the primary structure of a biomolecule. In the case of proteins, a region is defined by a contiguous portion of the amino acid sequence of that protein.

The term "domain" is herein defined as referring to a structural part of a biomolecule that contributes to a known or suspected function of the biomolecule. Domains may be co-extensive with regions or portions thereof; domains may also incorporate a portion of a biomolecule that is distinct from a particular region, in addition to all or part of that region . Examples of GPCR protein domains include, but are not limited to, the extracellular (*i.e.*, N-terminal), transmembrane and cytoplasmic (*i.e.*, C-terminal) domains, which are co-extensive with like-named regions of GPCRs; each of the seven transmembrane segments of a GPCR; and each of the loop segments (both extracellular and intracellular loops) connecting adjacent transmembrane segments.

As used herein, the term "activity" refers to a variety of measurable indicia suggesting or revealing binding, either direct or indirect; affecting a response, i.e. having a measurable affect in response to some exposure or stimulus, including, for example, the affinity of a compound for directly binding a polypeptide or polynucleotide of the invention, or, for example, measurement of amounts of upstream or downstream proteins or other similar functions after some stimulus or event.

Unless indicated otherwise, as used herein, the abbreviation in lower case (gpcr) refers to a gene, cDNA, RNA or nucleic acid sequence, while the upper case version (GPCR) refers to a protein, polypeptide, peptide, oligopeptide, or amino acid sequence. The term "nGPCR-x" refers to any of the nGPCRs taught herein, while specific reference to a nGPCR (for example nGPCR-2073) refers only to that specific nGPCR.

As used herein, the term "antibody" is meant to refer to complete, intact antibodies, and Fab, Fab', F(ab)2, and other fragments thereof. Complete, intact

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antibodies include monoclonal antibodies such as murine monoclonal antibodies, chimeric antibodies and humanized antibodies.

As used herein, the term "binding" means the physical or chemical interaction between two proteins or compounds or associated proteins or compounds or combinations thereof. Binding includes ionic, non-ionic, Hydrogen bonds, Van der Waals, hydrophobic interactions, etc. The physical interaction, the binding, can be either direct or indirect, indirect being through or due to the effects of another protein or compound. Direct binding refers to interactions that do not take place through or due to the effect of another protein or compound but instead are without other substantial chemical intermediates. Binding may be detected in many different manners. As a non-limiting example, the physical binding interaction between a nGPCR-x of the invention and a compound can be detected using a labeled compound. Alternatively, functional evidence of binding can be detected using, for example, a cell transfected with and expressing a nGPCR-x of the invention. Binding of the transfected cell to a ligand of the nGPCR-x that was transfected into the cell provides functional evidence of binding. Other methods of detecting binding are well known to those of skill in the art.

As used herein, the term "compound" means any identifiable chemical or molecule, including, but not limited to, small molecule, peptide, protein, sugar, nucleotide, or nucleic acid, and such compound can be natural or synthetic.

As used herein, the term "complementary" refers to Watson-Crick basepairing between nucleotide units of a nucleic acid molecule.

As used herein, the term "contacting" means bringing together, either directly or indirectly, a compound into physical proximity to a polypeptide or polynucleotide of the invention. The polypeptide or polynucleotide can be in any number of buffers, salts, solutions *etc.* Contacting includes, for example, placing the compound into a beaker, microtiter plate, cell culture flask, or a microarray, such as a gene chip, or the like, which contains the nucleic acid molecule, or polypeptide encoding the nGPCR or fragment thereof.

As used herein, the phrase "homologous nucleotide sequence," or "homologous amino acid sequence," or variations thereof, refers to sequences characterized by a homology, at the nucleotide level or amino acid level, of at least the specified percentage.

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Homologous nucleotide sequences include those sequences coding for isoforms of proteins. Such isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. Homologous nucleotide sequences include nucleotide sequences encoding for a protein of a species other than humans, including, but not limited to, mammals. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the nucleotide sequence encoding other known GPCRs. Homologous amino acid sequences include those amino acid sequences which contain conservative amino acid substitutions and which polypeptides have the same binding and/or activity. A homologous amino acid sequence does not, however, include the amino acid sequence encoding other known GPCRs. Percent homology can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison WI), using the default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482-489, which is incorporated herein by reference in its entirety).

As used herein, the term "isolated" nucleic acid molecule refers to a nucleic acid molecule (DNA or RNA) that has been removed from its native environment. Examples of isolated nucleic acid molecules include, but are not limited to, recombinant DNA molecules contained in a vector, recombinant DNA molecules maintained in a heterologous host cell, partially or substantially purified nucleic acid molecules, and synthetic DNA or RNA molecules.

As used herein, the terms "modulates" or "modifies" means an increase or decrease in the amount, quality, or effect of a particular activity or protein.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues which has a sufficient number of bases to be used in a polymerase chain reaction (PCR). This short sequence is based on (or designed from) a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a DNA sequence having at least about 10 nucleotides and as many as about 50

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nucleotides, preferably about 15 to 30 nucleotides. They are chemically synthesized and may be used as probes.

As used herein, the term "probe" refers to nucleic acid sequences of variable length, preferably between at least about 10 and as many as about 6,000 nucleotides, depending on use. They are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. They may be single- or double-stranded and carefully designed to have specificity in PCR, hybridization membrane-based, or ELISA-like technologies.

The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.

The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (*i.e.*, slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, cell signaling, or cell survival. An abnormal condition may also include obesity, diabetic complications such as retinal degeneration, and irregularities in glucose uptake and metabolism, and fatty acid uptake and metabolism.

Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.

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Abnormal differentiation conditions include, but are not limited to, neurodegenerative disorders, slow wound healing rates, and slow tissue grafting healing rates. Abnormal cell signaling conditions include, but are not limited to, psychiatric disorders involving excess neurotransmitter activity.

Abnormal cell survival conditions may also relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques and carrier techniques.

The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig or goat, more preferably a monkey or ape, and most preferably a human.

By "amplification" it is meant increased numbers of DNA or RNA in a cell compared with normal cells. "Amplification" as it refers to RNA can be the detectable presence of RNA in cells, since in some normal cells there is no basal expression of RNA. In other normal cells, a basal level of expression exists, therefore in these cases amplification is the detection of at least 1 to 2-fold, and preferably more, compared to the basal level.

As used herein, the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a probe, primer, or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are

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sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present in excess, at T_m, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (e.g. 10 to 50 nucleotides) and at least about 60°C for longer probes, primers or oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

The amino acid sequences are presented in the amino to carboxy direction, from left to right. The amino and carboxy groups are not presented in the sequence. The nucleotide sequences are presented by single strand only, in the 5' to 3' direction, from left to right. Nucleotides and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission or (for amino acids) by three letters code.

Polynucleotides

The present invention provides purified and isolated polynucleotides (*e.g.*, DNA sequences and RNA transcripts, both sense and complementary antisense strands, both single- and double-stranded, including splice variants thereof) that encode unknown G protein-coupled receptors heretofore termed novel GPCRs, or nGPCRs. These genes are described herein and designated herein collectively as nGPCR-x (where x is 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2230, 2231, 2232, 2233. 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2310, 2311, 2312, 2313,

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2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, and 2355). Table 1 below identifies the novel gene sequence nGPCR-x designation, the SEQ ID NO: of the gene sequence, the SEQ ID NO: of the polypeptide encoded thereby, and the U.S. Provisional Application in which the gene sequence has been disclosed.

Table 1

nGPCR	Nucleotide Sequence (SEQ ID NO:)	Amino acid Sequence (SEQ ID NO:)	Originally filed in:	nGCPR	Nucleotide Sequence (SEQ ID NO:)	Amino acid Sequence (SEQ ID NO:)	Originally filed in:
2157	1	121	A	2287	61	181	G
2158	2	122	A	2288	62	182	G
2159	3	123	A	2289	63	183	G
2160	4	124	A	2290	64	184	G
2161	5	125	A	2291	65	185	G
2162	6	126	A	2292	66	186	G
2163	7	127	A	2293	67	187	G
2164	8	128	A	2294	68	188	G
2165	9	129	A	2295	69	189	G
2166	10	130	A	2296	70	190	G
2230	11	131	B	2297	71	191	H
2231	12	132	B	2298	72	192	H
2232	13	133	B	2299	73	193	H
2233	14	134	B	2300	74	194	H
2234	15	135	B	2301	75	195	H
2235	16	136	B	2302	76	196	H
2236	17	137	B	2303	77	197	H
2237	18	138	B	2304	78	198	H
2238	19	139	B	2305	79	199	H
2239	20	140	B	2306	80	200	H
2240	21	141	C	2307	81	201	I
2241	22	142	C	2308	82	202	I
2242	23	143	C	2309	83	203	I
2243	24	144	C	2310	84	204	I
2244	25	145	C	2311	85	205	I
2245	26	146	C	2312	86	206	I
2246	27	147	C	2313	87	207	I
2247	28	148	C	2314	88	208	I
2248	29	149	C	2315	89	209	I
2249	30	150	C	2316	90	210	I
2250	31	151	D	2317	91	211	J
2251	32	142	D	2318	92	212	J
2252	33	153	D	2319	93	213	J
2253	34	154	D	2320	94	214	J
2254	35	155	D	2321	95	215	J
2255	36	156	D	2322	96	216	J
2256	37	157	D	2323	97	217	J
2257	38	158	D	2324	98	218	J
2258	39	159	D	2325	99	219	J
2259	40	160	D	2326	100	220	J
2260	41	161	E	2327	101	221	K

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2261	42	162	E	2328	102	222	K
2262	43	163	E	2329	103	223	K
2263	44	164	E	2330	104	224	K
2264	45	165	E	2331	105	225	K
2265	46	166	E	2332	106	226	K
2266	47	167	E	2333	107	227	K
2267	48	168	E	2334	108	228	K
2268	49	169	E	2335	109	229	K
2269	50	170	E	2336	110	230	K
2270	51	171	F	2346	111	231	L
2271	52	172	F	2347	112	232	L
2272	53	173	F	2348	113	233	L
2273	54	174	F	2349	114	234	L
2274	55	175	F	2350	115	235	L
2275	56	176	F	2351	116	236	L
2276	57	177	F	2352	117	237	L
2277	58	178	F	2353	118	238	L
2278	59	179	F	2354	119	239	L
2279	60	180	F	2355	120	240	L

Legend

A= Ser. No. 60/187,584
B= Ser. No. 60/187,707
C= Ser. No. 60/187,708
D= Ser. No. 60/188,290
E= Ser. No. 60/188,292
F= Ser. No. 60/187,827
G= Ser. No. 60/188,293
H= Ser. No. 60/187,639
I= Ser. No. 60/187,583
J= Ser. No. 60/187,709
K= Ser. No. 60/187,637
L= Ser. No. 60/187,640

When a specific nGPCR is identified (for example nGPCR-2270), it is understood that only that specific nGPCR is being referred to.

It is well known that GCPRs are expressed in many different tissues, including the brain. Accordingly, the nGPCR-x of the present invention may be useful, *inter alia*, for treating and/or diagnosing mental disorders. Following the techniques described in Example 5, below, those skilled in the art could readily ascertain if nGPCR-x is expressed in a particular tissue or region.

The invention provides purified and isolated polynucleotides (*e.g.*, cDNA, genomic DNA, synthetic DNA, RNA, or combinations thereof, whether single- or double-stranded) that comprise a nucleotide sequence encoding the amino acid sequence of the polypeptides of the invention. Such polynucleotides are useful for recombinantly expressing the receptor and also for detecting expression of the receptor in cells (*e.g.*, using Northern hybridization and *in situ* hybridization assays). Such polynucleotides also are useful in the design of antisense and other molecules for the suppression of the expression of nGPCR-x in a cultured cell, a tissue, or an animal; for therapeutic purposes; or to provide a model for diseases or conditions characterized by aberrant nGPCR-x expression. Specifically

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excluded from the definition of polynucleotides of the invention are entire isolated, non-recombinant native chromosomes of host cells. A preferred polynucleotide has a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, which correspond to naturally occurring nGPCR-x sequences. It will be appreciated that numerous other polynucleotide sequences exist that also encode nGPCR-x having the sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, due to the well-known degeneracy of the universal genetic code.

The invention also provides a purified and isolated polynucleotide comprising a nucleotide sequence that encodes a mammalian polypeptide, wherein the polynucleotide hybridizes to a polynucleotide having the sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or the non-coding strand complementary thereto, under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate; and

(b) washing 2 times for 30 minutes each at 60°C in a wash solution comprising 0.1% SSC, 1% SDS. Polynucleotides that encode a human allelic variant are highly preferred.

The present invention relates to molecules which comprise the gene sequences that encode the nGPCRs; constructs and recombinant host cells incorporating the gene sequences; the novel GPCR polypeptides encoded by the gene sequences; antibodies to the polypeptides and homologs; kits employing the polynucleotides and polypeptides, and methods of making and using all of the foregoing. In addition, the present invention relates to homologs of the gene sequences and of the polypeptides and methods of making and using the same.

Genomic DNA of the invention comprises the protein-coding region for a polypeptide of the invention and is also intended to include allelic variants thereof. It is widely understood that, for many genes, genomic DNA is transcribed into RNA transcripts that undergo one or more splicing events wherein intron (*i.e.,* non-coding regions) of the transcripts are removed, or "spliced out." RNA transcripts that can be spliced by alternative mechanisms, and therefore be subject to removal of different RNA sequences but still encode a nGPCR-x polypeptide, are referred to in the art as splice variants which

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are embraced by the invention. Splice variants comprehended by the invention therefore are encoded by the same original genomic DNA sequences but arise from distinct mRNA transcripts. Allelic variants are modified forms of a wild-type gene sequence, the modification resulting from recombination during chromosomal segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are naturally occurring sequences (as opposed to non-naturally occurring variants that arise from *in vitro* manipulation).

The invention also comprehends cDNA that is obtained through reverse transcription of an RNA polynucleotide encoding nGPCR-x (conventionally followed by second strand synthesis of a complementary strand to provide a double-stranded DNA).

Preferred DNA sequences encoding human nGPCR-x polypeptides are selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120. A preferred DNA of the invention comprises a double stranded molecule along with the complementary molecule (the "non-coding strand" or "complement") having a sequence unambiguously deducible from the coding strand according to Watson-Crick base-pairing rules for DNA. Also preferred are other polynucleotides encoding the nGPCR-x polypeptide selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, which differ in sequence from the polynucleotides selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, by virtue of the well-known degeneracy of the universal nuclear genetic code.

The invention further embraces other species, preferably mammalian, homologs of the human nGPCR-x DNA. Species homologs, sometimes referred to as "orthologs," in general, share at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% homology with human DNA of the invention. Generally, percent sequence "homology" with respect to polynucleotides of the invention may be calculated as the percentage of nucleotide bases in the candidate sequence that are identical to nucleotides in the nGPCR-x sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity.

Polynucleotides of the invention permit identification and isolation of polynucleotides encoding related nGPCR-x polypeptides, such as human allelic variants

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and species homologs, by well-known techniques including Southern and/or Northern hybridization, and polymerase chain reaction (PCR). Examples of related polynucleotides include human and non-human genomic sequences, including allelic variants, as well as polynucleotides encoding polypeptides homologous to nGPCR-x and structurally related polypeptides sharing one or more biological, immunological, and/or physical properties of nGPCR-x. Non-human species genes encoding proteins homologous to nGPCR-x can also be identified by Southern and/or PCR analysis and are useful in animal models for nGPCR-x disorders. Knowledge of the sequence of a human nGPCR-x DNA also makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding nGPCR-x expression control regulatory sequences such as promoters, operators, enhancers, repressors, and the like. Polynucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express nGPCR-x. Polynucleotides of the invention may also provide a basis for diagnostic methods useful for identifying a genetic alteration(s) in a nGPCR-x locus that underlies a disease state or states, which information is useful both for diagnosis and for selection of therapeutic strategies.

According to the present invention, the nGPCR-x nucleotide sequences disclosed herein may be used to identify homologs of the nGPCR-x, in other animals, including but not limited to humans and other mammals, and invertebrates. Any of the nucleotide sequences disclosed herein, or any portion thereof, can be used, for example, as probes to screen databases or nucleic acid libraries, such as, for example, genomic or cDNA libraries, to identify homologs, using screening procedures well known to those skilled in the art. Accordingly, homologs having at least 50%, more preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably at least 95%, and most preferably at least 100% homology with nGPCR-x sequences can be identified.

The disclosure herein of full-length polynucleotides encoding nGPCR-x polypeptides makes readily available to the worker of ordinary skill in the art every possible fragment of the full-length polynucleotide.

One preferred embodiment of the present invention provides an isolated nucleic acid molecule comprising a sequence homologous sequences selected from the group

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consisting of SEQ ID NO:1 to SEQ ID NO:120, and fragments thereof. Another preferred embodiment provides an isolated nucleic acid molecule comprising a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, and fragments thereof.

As used in the present invention, fragments of nGPCR-x-encoding polynucleotides comprise at least 10, and preferably at least 12, 14, 16, 18, 20, 25, 50, or 75 consecutive nucleotides of a polynucleotide encoding nGPCR-x. Preferably, fragment polynucleotides of the invention comprise sequences unique to the nGPCR-x-encoding polynucleotide sequence, and therefore hybridize under highly stringent or moderately stringent conditions only (*i.e.*, "specifically") to polynucleotides encoding nGPCR-x (or fragments thereof). Polynucleotide fragments of genomic sequences of the invention comprise not only sequences unique to the coding region, but also include fragments of the full-length sequence derived from introns, regulatory regions, and/or other non-translated sequences. Sequences unique to polynucleotides of the invention are recognizable through sequence comparison to other known polynucleotides, and can be identified through use of alignment programs routinely utilized in the art, *e.g.*, those made available in public sequence databases. Such sequences also are recognizable from Southern hybridization analyses to determine the number of fragments of genomic DNA to which a polynucleotide will hybridize. Polynucleotides of the invention can be labeled in a manner that permits their detection, including radioactive, fluorescent, and enzymatic labeling.

Fragment polynucleotides are particularly useful as probes for detection of full-length or fragments of nGPCR-x polynucleotides. One or more polynucleotides can be included in kits that are used to detect the presence of a polynucleotide encoding nGPCR-x, or used to detect variations in a polynucleotide sequence encoding nGPCR-x.

The invention also embraces DNAs encoding nGPCR-x polypeptides that hybridize under moderately stringent or high stringency conditions to the non-coding strand, or complement, of the polynucleotides set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120.

Exemplary highly stringent hybridization conditions are as follows: hybridization at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% Dextran sulfate, and washing twice for 30 minutes at 60°C in a wash solution comprising

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0.1X SSC and 1% SDS. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel *et al.* (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

With the knowledge of the nucleotide sequence information disclosed in the present invention, one skilled in the art can identify and obtain nucleotide sequences which encode nGPCR-x from different sources (*i.e.*, different tissues or different organisms) through a variety of means well known to the skilled artisan and as disclosed by, for example, Sambrook et al., "Molecular cloning: a laboratory manual", Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), which is incorporated herein by reference in its entirety.

For example, DNA that encodes nGPCR-x may be obtained by screening of mRNA, cDNA, or genomic DNA with oligonucleotide probes generated from the nGPCR-x gene sequence information provided herein. Probes may be labeled with a detectable group, such as a fluorescent group, a radioactive atom or a chemiluminescent group in accordance with procedures known to the skilled artisan and used in conventional hybridization assays, as described by, for example, Sambrook *et al.*

A nucleic acid molecule comprising any of the nGPCR-x nucleotide sequences described above can alternatively be synthesized by use of the polymerase chain reaction (PCR) procedure, with the PCR oligonucleotide primers produced from the nucleotide sequences provided herein. See U.S. Patent Numbers 4,683,195 to Mullis *et al.* and 4,683,202 to Mullis. The PCR reaction provides a method for selectively increasing the concentration of a particular nucleic acid sequence even when that sequence has not been previously purified and is present only in a single copy in a particular sample. The method can be used to amplify either single- or double-stranded DNA. The essence of the method

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involves the use of two oligonucleotide probes to serve as primers for the template-dependent, polymerase mediated replication of a desired nucleic acid molecule.

A wide variety of alternative cloning and *in vitro* amplification methodologies are well known to those skilled in the art. Examples of these techniques are found in, for example, Berger *et al.*, *Guide to Molecular Cloning Techniques*, Methods in Enzymology 152, Academic Press, Inc., San Diego, CA (Berger), which is incorporated herein by reference in its entirety.

Automated sequencing methods can be used to obtain or verify the nucleotide sequence of nGPCR-x. The nGPCR-x nucleotide sequences of the present invention are believed to be 100% accurate. However, as is known in the art, nucleotide sequence obtained by automated methods may contain some errors. Nucleotide sequences determined by automation are typically at least about 90%, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of a given nucleic acid molecule. The actual sequence may be more precisely determined using manual sequencing methods, which are well known in the art. An error in a sequence which results in an insertion or deletion of one or more nucleotides may result in a frame shift in translation such that the predicted amino acid sequence will differ from that which would be predicted from the actual nucleotide sequence of the nucleic acid molecule, starting at the point of the mutation.

The nucleic acid molecules of the present invention, and fragments derived therefrom, are useful for screening for restriction fragment length polymorphism (RFLP) associated with certain disorders, as well as for genetic mapping.

The polynucleotide sequence information provided by the invention makes possible large-scale expression of the encoded polypeptide by techniques well known and routinely practiced in the art.

Vectors

Another aspect of the present invention is directed to vectors, or recombinant expression vectors, comprising any of the nucleic acid molecules described above. Vectors are used herein either to amplify DNA or RNA encoding nGPCR-x and/or to express DNA which encodes nGPCR-x. Preferred vectors include, but are not limited to, plasmids, phages, cosmids, episomes, viral particles or viruses, and integratable DNA

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fragments (*i.e.*, fragments integratable into the host genome by homologous recombination). Preferred viral particles include, but are not limited to, adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses. Preferred expression vectors include, but are not limited to, pcDNA3 (Invitrogen) and pSVL (Pharmacia Biotech). Other expression vectors include, but are not limited to, pSPORT™ vectors, pGEM™ vectors (Promega), pPROEXvectors™ (LTI, Bethesda, MD), Bluescript™ vectors (Stratagene), pQE™ vectors (Qiagen), pSE420™ (Invitrogen), and pYES2™(Invitrogen).

Expression constructs preferably comprise GPCR-x-encoding polynucleotides operatively linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator. Expression control DNA sequences include promoters, enhancers, operators, and regulatory element binding sites generally, and are typically selected based on the expression systems in which the expression construct is to be utilized. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Expression constructs may also include sequences that facilitate, and preferably promote, homologous recombination in a host cell. Preferred constructs of the invention also include sequences necessary for replication in a host cell.

Expression constructs are preferably utilized for production of an encoded protein, but may also be utilized simply to amplify a nGPCR-x-encoding polynucleotide sequence. In preferred embodiments, the vector is an expression vector wherein the polynucleotide of the invention is operatively linked to a polynucleotide comprising an expression control sequence. Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating polynucleotides of the invention are also provided. Preferred expression vectors are replicable DNA constructs in which a DNA sequence encoding nGPCR-x is operably linked or connected to suitable control sequences capable of effecting the expression of the nGPCR-x in a suitable host. DNA regions are operably linked or connected when they are functionally related to each other. For example, a promoter is operably linked or connected to a coding sequence if it controls the

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transcription of the sequence. Amplification vectors do not require expression control domains, but rather need only the ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants. The need for control sequences in the expression vector will vary depending upon the host selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding and sequences which control the termination of transcription and translation.

Preferred vectors preferably contain a promoter that is recognized by the host organism. The promoter sequences of the present invention may be prokaryotic, eukaryotic or viral. Examples of suitable prokaryotic sequences include the P_R and P_L promoters of bacteriophage lambda (The bacteriophage Lambda, Hershey, A. D., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1973), which is incorporated herein by reference in its entirety; Lambda II, Hendrix, R. W., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1980), which is incorporated herein by reference in its entirety); the trp, recA, heat shock, and lacZ promoters of *E. coli* and the SV40 early promoter (Benoist *et al. Nature*, 1981, *290*, 304-310, which is incorporated herein by reference in its entirety). Additional promoters include, but are not limited to, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, Rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein.

Additional regulatory sequences can also be included in preferred vectors. Preferred examples of suitable regulatory sequences are represented by the Shine-Dalgarno of the replicase gene of the phage MS-2 and of the gene cII of bacteriophage lambda. The Shine-Dalgarno sequence may be directly followed by DNA encoding nGPCR-x and result in the expression of the mature nGPCR-x protein.

Moreover, suitable expression vectors can include an appropriate marker that allows the screening of the transformed host cells. The transformation of the selected host is carried out using any one of the various techniques well known to the expert in the art and described in Sambrook *et al., supra*.

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An origin of replication can also be provided either by construction of the vector to include an exogenous origin or may be provided by the host cell chromosomal replication mechanism. If the vector is integrated into the host cell chromosome, the latter may be sufficient. Alternatively, rather than using vectors which contain viral origins of replication, one skilled in the art can transform mammalian cells by the method of co-transformation with a selectable marker and nGPCR-x DNA. An example of a suitable marker is dihydrofolate reductase (DHFR) or thymidine kinase (*see*, U.S. Patent No. 4,399,216).

Nucleotide sequences encoding GPCR-x may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesiderable joining, and ligation with appropriate ligases. Techniques for such manipulation are disclosed by Sambrook et al., *supra* and are well known in the art. Methods for construction of mammalian expression vectors are disclosed in, for example, Okayama *et al.*, *Mol. Cell. Biol.*, **1983**, *3*, 280, Cosman *et al.*, *Mol. Immunol.*, **1986**, *23*, 935, Cosman *et al.*, *Nature*, **1984**, *312*, 768, EP-A-0367566, and WO 91/18982, each of which is incorporated herein by reference in its entirety.

Host cells

According to another aspect of the invention, host cells are provided, including prokaryotic and eukaryotic cells, comprising a polynucleotide of the invention (or vector of the invention) in a manner that permits expression of the encoded nGPCR-x polypeptide. Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell that are well known and routinely practiced in the art include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant, insect, invertebrate, vertebrate, and mammalian cells systems.

The invention provides host cells that are transformed or transfected (stably or transiently) with polynucleotides of the invention or vectors of the invention. As stated

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above, such host cells are useful for amplifying the polynucleotides and also for expressing the nGPCR-x polypeptide or fragment thereof encoded by the polynucleotide.

In still another related embodiment, the invention provides a method for producing a nGPCR-x polypeptide (or fragment thereof) comprising the steps of growing a host cell of the invention in a nutrient medium and isolating the polypeptide or variant thereof from the cell or the medium. Because nGPCR-x is a seven transmembrane receptor, it will be appreciated that, for some applications, such as certain activity assays, the preferable isolation may involve isolation of cell membranes containing the polypeptide embedded therein, whereas for other applications a more complete isolation may be preferable.

According to some aspects of the present invention, transformed host cells having an expression vector comprising any of the nucleic acid molecules described above are provided. Expression of the nucleotide sequence occurs when the expression vector is introduced into an appropriate host cell. Suitable host cells for expression of the polypeptides of the invention include, but are not limited to, prokaryotes, yeast, and eukaryotes. If a prokaryotic expression vector is employed, then the appropriate host cell would be any prokaryotic cell capable of expressing the cloned sequences. Suitable prokaryotic cells include, but are not limited to, bacteria of the genera *Escherichia*, *Bacillus*, *Salmonella*, *Pseudomonas*, *Streptomyces*, and *Staphylococcus*.

If an eukaryotic expression vector is employed, then the appropriate host cell would be any eukaryotic cell capable of expressing the cloned sequence. Preferably, eukaryotic cells are cells of higher eukaryotes. Suitable eukaryotic cells include, but are not limited to, non-human mammalian tissue culture cells and human tissue culture cells. Preferred host cells include, but are not limited to, insect cells, HeLa cells, Chinese hamster ovary cells (CHO cells), African green monkey kidney cells (COS cells), human HEK-293 cells, and murine 3T3 fibroblasts. Propagation of such cells in cell culture has become a routine procedure (*see*, Tissue Culture, Academic Press, Kruse and Patterson, eds. (1973), which is incorporated herein by reference in its entirety).

In addition, a yeast host may be employed as a host cell. Preferred yeast cells include, but are not limited to, the genera *Saccharomyces*, *Pichia*, and *Kluveromyces*. Preferred yeast hosts are *S. cerevisiae* and *P. pastoris*. Preferred yeast vectors can contain an origin of replication sequence from a 2T yeast plasmid, an autonomously replication

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sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Shuttle vectors for replication in both yeast and *E. coli* are also included herein.

Alternatively, insect cells may be used as host cells. In a preferred embodiment, the polypeptides of the invention are expressed using a baculovirus expression system (*see*, Luckow *et al.*, *Bio/Technology*, **1988**, *6*, 47, Baculovirus Expression Vectors: A Laboratory Manual, O'Rielly *et al.* (Eds.), W.H. Freeman and Company, New York, 1992, and U.S. Patent No. 4,879,236, each of which is incorporated herein by reference in its entirety). In addition, the MAXBAC™ complete baculovirus expression system (Invitrogen) can, for example, be used for production in insect cells.

Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with nGPCR-x. Host cells of the invention are also useful in methods for the large-scale production of nGPCR-x polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells, or from the medium in which the cells are grown, by purification methods known in the art, *e.g.*, conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC, and the like. Still other methods of purification include those methods wherein the desired protein is expressed and purified as a fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or can be left as an intact fusion protein. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues as a result of the cleavage process.

Knowledge of nGPCR-x DNA sequences allows for modification of cells to permit, or increase, expression of endogenous nGPCR-x. Cells can be modified (*e.g*, by homologous recombination) to provide increased expression by replacing, in whole or in part, the naturally occurring nGPCR-x promoter with all or part of a heterologous promoter so that the cells express nGPCR-x at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to endogenous nGPCR-x encoding

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sequences. (See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955.) It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, ada, dhfr, and the multifunctional CAD gene which encodes carbamoyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the nGPCR-x coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the nGPCR-x coding sequences in the cells.

Knock-outs

The DNA sequence information provided by the present invention also makes possible the development (*e.g.*, by homologous recombination or "knock-out" strategies; see Capecchi, *Science 244*:1288-1292 (1989), which is incorporated herein by reference) of animals that fail to express functional nGPCR-x or that express a variant of nGPCR-x. Such animals (especially small laboratory animals such as rats, rabbits, and mice) are useful as models for studying the *in vivo* activities of nGPCR-x and modulators of nGPCR-x.

Antisense

Also made available by the invention are anti-sense polynucleotides that recognize and hybridize to polynucleotides encoding nGPCR-x. Full-length and fragment anti-sense polynucleotides are provided. Fragment antisense molecules of the invention include (i) those that specifically recognize and hybridize to nGPCR-x RNA (as determined by sequence comparison of DNA encoding nGPCR-x to DNA encoding other known molecules). Identification of sequences unique to nGPCR-x encoding polynucleotides can be deduced through use of any publicly available sequence database, and/or through use of commercially available sequence comparison programs. After identification of the desired sequences, isolation through restriction digestion or amplification using any of the various polymerase chain reaction techniques well known in the art can be performed. Anti-sense polynucleotides are particularly relevant to regulating expression of nGPCR-x by those cells expressing nGPCR-x mRNA.

Antisense nucleic acids (preferably 10 to 30 base-pair oligonucleotides) capable of specifically binding to nGPCR-x expression control sequences or nGPCR-x RNA are

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introduced into cells (*e.g.*, by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the nGPCR-x target nucleotide sequence in the cell and prevents transcription and/or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by adding poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end. Suppression of nGPCR-x expression at either the transcriptional or translational level is useful to generate cellular or animal models for diseases/conditions characterized by aberrant nGPCR-x expression.

Antisense oligonucleotides, or fragments of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or sequences complementary or homologous thereto, derived from the nucleotide sequences of the present invention encoding nGPCR-x are useful as diagnostic tools for probing gene expression in various tissues. For example, tissue can be probed *in situ* with oligonucleotide probes carrying detectable groups by conventional autoradiography techniques to investigate native expression of this enzyme or pathological conditions relating thereto. Antisense oligonucleotides are preferably directed to regulatory regions of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or mRNA corresponding thereto, including, but not limited to, the initiation codon, TATA box, enhancer sequences, and the like.

Transcription factors

The nGPCR-x sequences taught in the present invention facilitate the design of novel transcription factors for modulating nGPCR-x expression in native cells and animals, and cells transformed or transfected with nGPCR-x polynucleotides. For example, the Cys_2-His_2 zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular nGPCR-x target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-

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based modeling and screening of phage display libraries (Segal *et al.*, Proc. Natl. Acad. Sci. (USA) 96:2758-2763 (1999); Liu *et al.*, Proc. Natl. Acad. Sci. (USA) 94:5525-5530 (1997); Greisman *et al.*, Science 275:657-661 (1997); Choo *et al.*, J. Mol. Biol. 273:525-532 (1997)). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal *et al.*) The artificial zinc finger repeats, designed based on nGPCR-x sequences, are fused to activation or repression domains to promote or suppress nGPCR-x expression (Liu *et al.)* Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim *et al.*, Proc. Natl. Acad. Sci. (USA) 94:3616-3620 (1997). Such proteins and polynucleotides that encode them, have utility for modulating nGPCR-x expression *in vivo* in both native cells, animals and humans; and/or cells transfected with nGPCR-x-encoding sequences. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods (McColl *et al.*, Proc. Natl. Acad. Sci. (USA) 96:9521-9526 (1997); Wu *et al.*, Proc. Natl. Acad. Sci. (USA) 92:344-348 (1995)). The present invention contemplates methods of designing such transcription factors based on the gene sequence of the invention, as well as customized zinc finger proteins, that are useful to modulate nGPCR-x expression in cells (native or transformed) whose genetic complement includes these sequences.

Polypeptides

The invention also provides purified and isolated mammalian nGPCR-x polypeptides encoded by a polynucleotide of the invention. Presently preferred is a human nGPCR-x polypeptide comprising the amino acid sequence set out in sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, or fragments thereof comprising an epitope specific to the polypeptide. By "epitope specific to" is meant a

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portion of the nGPCR receptor that is recognizable by an antibody that is specific for the nGPCR, as defined in detail below.

Although the sequences provided are particular human sequences, the invention is intended to include within its scope other human allelic variants; non-human mammalian forms of nGPCR-x, and other vertebrate forms of nGPCR-x.

It will be appreciated that extracellular epitopes are particularly useful for generating and screening for antibodies and other binding compounds that bind to receptors such as nGPCR-x. Thus, in another preferred embodiment, the invention provides a purified and isolated polypeptide comprising at least one extracellular domain (*e.g.*, the N-terminal extracellular domain or one of the three extracellular loops) of nGPCR-x. Purified and isolated polypeptides comprising the N-terminal extracellular domain of nGPCR-x are highly preferred. Also preferred is a purified and isolated polypeptide comprising a nGPCR-x fragment selected from the group consisting of the N-terminal extracellular domain of nGPCR-x, transmembrane domains of nGPCR-x, an extracellular loop connecting transmembrane domains of nGPCR-x, an intracellular loop connecting transmembrane domains of nGPCR-x, the C-terminal cytoplasmic region of nGPCR-x, and fusions thereof. Such fragments may be continuous portions of the native receptor. However, it will also be appreciated that knowledge of the nGPCR-x gene and protein sequences as provided herein permits recombining of various domains that are not contiguous in the native protein. Using a FORTRAN computer program called "tmtrest.all" [Parodi *et al.*, Comput. Appl. Biosci. 5:527-535 (1994)], nGPCR-x was shown to contain transmembrane-spanning domains.

The invention also embraces polypeptides that have at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55% or at least 50% identity and/or homology to the preferred polypeptide of the invention. Percent amino acid sequence "identity" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptide

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of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

In one aspect, percent homology is calculated as the percentage of amino acid residues in the smaller of two sequences which align with identical amino acid residue in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment (Dayhoff, in Atlas of Protein Sequence and Structure, Vol. 5, p. 124, National Biochemical Research Foundation, Washington, D.C. (1972), incorporated herein by reference).

Polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. Use of mammalian host cells is expected to provide for such post-translational modifications (*e.g.*, glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated forms of nGPCR-x polypeptides are embraced by the invention.

The invention also embraces variant (or analog) nGPCR-x polypeptides. In one example, insertion variants are provided wherein one or more amino acid residues supplement a nGPCR-x amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the nGPCR-x amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and proteins including amino acid tags or labels.

Insertion variants include nGPCR-x polypeptides wherein one or more amino acid residues are added to a nGPCR-x acid sequence or to a biologically active fragment thereof.

Variant products of the invention also include mature nGPCR-x products, *i.e.*, nGPCR-x products wherein leader or signal sequences are removed, with additional amino terminal residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived

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from specific proteins. nGPCR-x products with an additional methionine residue at position -1 (Met^{-1}-nGPCR-x) are contemplated, as are variants with additional methionine and lysine residues at positions -2 and -1 (Met^{-2}-Lys^{-1}-nGPCR-x). Variants of nGPCR-x with additional Met, Met-Lys, Lys residues (or one or more basic residues in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

The invention also embraces nGPCR-x variants having additional amino acid residues that result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of a glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at position -1 after cleavage of the GST component from the desired polypeptide. Variants that result from expression in other vector systems are also contemplated.

Insertional variants also include fusion proteins wherein the amino terminus and/or the carboxy terminus of nGPCR-x is/are fused to another polypeptide.

In another aspect, the invention provides deletion variants wherein one or more amino acid residues in a nGPCR-x polypeptide are removed. Deletions can be effected at one or both termini of the nGPCR-x polypeptide, or with removal of one or more non-terminal amino acid residues of nGPCR-x. Deletion variants, therefore, include all fragments of a nGPCR-x polypeptide.

The invention also embraces polypeptide fragments of sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, wherein the fragments maintain biological (*e.g.*, ligand binding and/or intracellular signaling) immunological properties of a nGPCR-x polypeptide.

In one preferred embodiment of the invention, an isolated nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and fragments thereof, wherein the nucleic acid molecule encoding at least a portion of nGPCR-x. In a more preferred embodiment, the isolated nucleic acid molecule comprises a sequence that encodes a polypeptide comprising sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and fragments thereof.

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As used in the present invention, polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, or 40 consecutive amino acids of sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240. Preferred polypeptide fragments display antigenic properties unique to, or specific for, human nGPCR-x and its allelic and species homologs. Fragments of the invention having the desired biological and immunological properties can be prepared by any of the methods well known and routinely practiced in the art.

In still another aspect, the invention provides substitution variants of nGPCR-x polypeptides. Substitution variants include those polypeptides wherein one or more amino acid residues of a nGPCR-x polypeptide are removed and replaced with alternative residues. In one aspect, the substitutions are conservative in nature; however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for this purpose may be defined as set out in Tables 2, 3, or 4 below.

Variant polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table 2 (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96), immediately below.

Table 2

Conservative Substitutions I

SIDE CHAIN CHARACTERISTIC	AMINO ACID
Aliphatic	
Non-polar	G A P I L V
Polar – uncharged	C S T M N Q
Polar – charged	D E K R
Aromatic	H F W Y
Other	N Q D E

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Alternatively, conservative amino acids can be grouped as described in Lehninger, [Biochemistry, Second Edition; Worth Publishers, Inc. NY, NY (1975), pp.71-77] as set out in Table 3, below.

Table 3
Conservative Substitutions II

SIDE CHAIN CHARACTERISTIC	AMINO ACID
Non-polar (hydrophobic)	
A. Aliphatic:	A L I V P
B. Aromatic:	F W
C. Sulfur-containing:	M
D. Borderline:	G
Uncharged-polar	
A. Hydroxyl:	S T Y
B. Amides:	N Q
C. Sulfhydryl:	C
D. Borderline:	G
Positively Charged (Basic):	K R H
Negatively Charged (Acidic):	D E

As still another alternative, exemplary conservative substitutions are set out in Table 4, below.

Table 4
Conservative Substitutions III

Original Residue	Exemplary Substitution
Ala (A)	Val, Leu, Ile
Arg (R)	Lys, Gln, Asn
Asn (N)	Gln, His, Lys, Arg
Asp (D)	Glu
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
His (H)	Asn, Gln, Lys, Arg
Ile (I)	Leu, Val, Met, Ala, Phe,
Leu (L)	Ile, Val, Met, Ala, Phe
Lys (K)	Arg, Gln, Asn
Met (M)	Leu, Phe, Ile
Phe (F)	Leu, Val, Ile, Ala
Pro (P)	Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr

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Tyr (Y)	Trp, Phe, Thr, Ser
Val (V)	Ile, Leu, Met, Phe, Ala

It should be understood that the definition of polypeptides of the invention is intended to include polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. By way of example, the modifications may be covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Such derivatives may be prepared to increase circulating half-life of a polypeptide, or may be designed to improve the targeting capacity of the polypeptide for desired cells, tissues, or organs. Similarly, the invention further embraces nGPCR-x polypeptides that have been covalently modified to include one or more water-soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

In a related embodiment, the present invention provides compositions comprising purified polypeptides of the invention. Preferred compositions comprise, in addition to the polypeptide of the invention, a pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluent that serves as a pharmaceutical vehicle, excipient, or medium. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, water, saline solutions, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, glycerol, calcium phosphate, mineral oil, and cocoa butter.

Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in assays of the invention and in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

The G protein-coupled receptor functions through a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) coupled to the intracellular

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portion of the G protein-coupled receptor molecule. Accordingly, the G protein-coupled receptor has a specific affinity to G protein. G proteins specifically bind to guanine nucleotides. Isolation of G proteins provides a means to isolate guanine nucleotides. G proteins may be isolated using commercially available anti-G protein antibodies or isolated G protein-coupled receptors. Similarly, G proteins may be detected in a sample isolated using commercially available detectable anti-G protein antibodies or isolated G protein-coupled receptors.

According to the present invention, the isolated nGPCR-x proteins of the present invention are useful to isolate and purify G proteins from samples such as cell lysates. Example 15 below sets forth an example of isolation of G proteins using isolated nGPCR-x proteins. Such methodolgy may be used in place of the use of commercially available anti-G protein antibodies which are used to isolate G proteins. Moreover, G proteins may be detected using n-GPCR-x proteins in place of commercially available detectable anti-G protein antibodies. Since nGPCR-x proteins specifically bind to G proteins, they can be employed in any specific use where G protein specific affinity is required such as those uses where commercially available anti-G protein antibodies are employed.

Antibodies

Also comprehended by the present invention are antibodies (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for nGPCR-x or fragments thereof. Preferred antibodies of the invention are human antibodies that are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', $F(ab')_2$, and F_v, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the invention recognize and bind nGPCR-x polypeptides exclusively (*i.e.*, are able to distinguish nGPCR-x polypeptides from other known GPCR polypeptides by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between

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nGPCR-x and such polypeptides). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and, in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow *et al.* (Eds.), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the nGPCR-x polypeptides of the invention are also contemplated, provided that the antibodies are specific for nGPCR-x polypeptides. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

The invention provides an antibody that is specific for the nGPCR-x of the invention. Antibody specificity is described in greater detail below. However, it should be emphasized that antibodies that can be generated from polypeptides that have previously been described in the literature and that are capable of fortuitously cross-reacting with nGPCR-x (*e.g.*, due to the fortuitous existence of a similar epitope in both polypeptides) are considered "cross-reactive" antibodies. Such cross-reactive antibodies are not antibodies that are "specific" for nGPCR-x. The determination of whether an antibody is specific for nGPCR-x or is cross-reactive with another known receptor is made using any of several assays, such as Western blotting assays, that are well known in the art. For identifying cells that express nGPCR-x and also for modulating nGPCR-x-ligand binding activity, antibodies that specifically bind to an extracellular epitope of the nGPCR-x are preferred.

In one preferred variation, the invention provides monoclonal antibodies. Hybridomas that produce such antibodies also are intended as aspects of the invention. In yet another variation, the invention provides a humanized antibody. Humanized antibodies are useful for *in vivo* therapeutic indications.

In another variation, the invention provides a cell-free composition comprising polyclonal antibodies, wherein at least one of the antibodies is an antibody of the invention specific for nGPCR-x. Antisera isolated from an animal is an exemplary composition, as

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is a composition comprising an antibody fraction of an antisera that has been resuspended in water or in another diluent, excipient, or carrier.

In still another related embodiment, the invention provides an anti-idiotypic antibody specific for an antibody that is specific for nGPCR-x.

It is well known that antibodies contain relatively small antigen binding domains that can be isolated chemically or by recombinant techniques. Such domains are useful nGPCR-x binding molecules themselves, and also may be reintroduced into human antibodies, or fused to toxins or other polypeptides. Thus, in still another embodiment, the invention provides a polypeptide comprising a fragment of a nGPCR-x-specific antibody, wherein the fragment and the polypeptide bind to the nGPCR-x. By way of non-limiting example, the invention provides polypeptides that are single chain antibodies and CDR-grafted antibodies.

Non-human antibodies may be humanized by any of the methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, *e.g.*, therapeutic purposes (by modulating activity of nGPCR-x), diagnostic purposes to detect or quantitate nGPCR-x, and purification of nGPCR-x. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific.

Compositions

Mutations in the nGPCR-x gene that result in loss of normal function of the nGPCR-x gene product underlie nGPCR-x-related human disease states. The invention comprehends gene therapy to restore nGPCR-x activity to treat those disease states. Delivery of a functional nGPCR-x gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, *Nature*, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, *Science, 244*: 1275-1281 (1989); Verma, *Scientific American*: 68-84

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(1990); and Miller, *Nature, 357*: 455-460 (1992). Alternatively, it is contemplated that in other human disease states, preventing the expression of, or inhibiting the activity of, nGPCR-x will be useful in treating disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of nGPCR-x.

Another aspect of the present invention is directed to compositions, including pharmaceutical compositions, comprising any of the nucleic acid molecules or recombinant expression vectors described above and an acceptable carrier or diluent. Preferably, the carrier or diluent is pharmaceutically acceptable. Suitable carriers are described in the most recent edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field, which is incorporated herein by reference in its entirety. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The formulations are sterilized by commonly used techniques.

Also within the scope of the invention are compositions comprising polypeptides, polynucleotides, or antibodies of the invention that have been formulated with, *e.g.*, a pharmaceutically acceptable carrier.

The invention also provides methods of using antibodies of the invention. For example, the invention provides a method for modulating ligand binding of a nGPCR-x comprising the step of contacting the nGPCR-x with an antibody specific for the nGPCR-x, under conditions wherein the antibody binds the receptor.

As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. GPCRs that may be expressed in the brain, such as nGPCR-x, provide an indication that aberrant nGPCR-x signaling activity may correlate with one or more neurological or psychological disorders. The invention also provides a method for treating a neurological or psychiatric disorder comprising the step of administering to a mammal in need of such treatment an amount of an antibody-like polypeptide of the invention that is sufficient to modulate ligand binding to a nGPCR-x in neurons of the mammal. nGPCR-x may also be expressed in other tissues, including but not limited to, peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, thyroid gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon,

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muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

Kits

The present invention is also directed to kits, including pharmaceutical kits. The kits can comprise any of the nucleic acid molecules described above, any of the polypeptides described above, or any antibody which binds to a polypeptide of the invention as described above, as well as a negative control. The kit preferably comprises additional components, such as, for example, instructions, solid support, reagents helpful for quantification, and the like.

In another aspect, the invention features methods for detection of a polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a polypeptide having sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, said probe comprising the nucleic acid sequence encoding the polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

In preferred embodiments of the invention, the disease is selected from the group consisting of thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial

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infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); and sexual dysfunction, among others.

Kits may be designed to detect either expression of polynucleotides encoding nGPCR-x expressed in the brain or the nGPCR-x proteins themselves in order to identify tissue as being neurological. For example, oligonucleotide hybridization kits can be provided which include a container having an oligonucleotide probe specific for the nGPCR-x-specific DNA and optionally, containers with positive and negative controls and/or instructions. Similarly, PCR kits can be provided which include a container having primers specific for the nGPCR-x-specific sequences, DNA and optionally, containers with size markers, positive and negative controls and/or instructions.

Hybridization conditions should be such that hybridization occurs only with the genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

The diseases for which detection of genes in a sample could be diagnostic include diseases in which nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells. By "amplification" is meant increased numbers of DNA or RNA in a cell compared with normal cells.

The diseases that could be diagnosed by detection of nucleic acid in a sample preferably include central nervous system and metabolic diseases. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

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Alternatively, immunoassay kits can be provided which have containers container having antibodies specific for the nGPCR-x-protein and optionally, containers with positive and negative controls and/or instructions.

Kits may also be provided useful in the identification of GPCR binding partners such as natural ligands or modulators (agonists or antagonists). Substances useful for treatment of disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question. Substances that modulate the activity of the polypeptides preferably include, but are not limited to, antisense oligonucleotides, agonists and antagonists, and inhibitors of protein kinases.

Methods of inducing immune response

Another aspect of the present invention is directed to methods of inducing an immune response in a mammal against a polypeptide of the invention by administering to the mammal an amount of the polypeptide sufficient to induce an immune response. The amount will be dependent on the animal species, size of the animal, and the like but can be determined by those skilled in the art.

Methods of identifying ligands

The invention also provides assays to identify compounds that bind nGPCR-x. One such assay comprises the steps of: (a) contacting a composition comprising a nGPCR-x with a compound suspected of binding nGPCR-x; and (b) measuring binding between the compound and nGPCR-x. In one variation, the composition comprises a cell expressing nGPCR-x on its surface. In another variation, isolated nGPCR-x or cell membranes comprising nGPCR-x are employed. The binding may be measured directly, *e.g.*, by using a labeled compound, or may be measured indirectly by several techniques, including measuring intracellular signaling of nGPCR-x induced by the compound (or measuring changes in the level of nGPCR-x signaling). Following steps (a) and (b), compounds identified as binding nGPCR-x may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x.

Specific binding molecules, including natural ligands and synthetic compounds, can be identified or developed using isolated or recombinant nGPCR-x products, nGPCR-x variants, or preferably, cells expressing such products. Binding partners are useful for

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purifying nGPCR-x products and detection or quantification of nGPCR-x products in fluid and tissue samples using known immunological procedures. Binding molecules are also manifestly useful in modulating (*i.e.*, blocking, inhibiting or stimulating) biological activities of nGPCR-x, especially those activities involved in signal transduction.

The DNA and amino acid sequence information provided by the present invention also makes possible identification of binding partner compounds with which a nGPCR-x polypeptide or polynucleotide will interact. Methods to identify binding partner compounds include solution assays, *in vitro* assays wherein nGPCR-x polypeptides are immobilized, and cell-based assays. Identification of binding partner compounds of nGPCR-x polypeptides provides candidates for therapeutic or prophylactic intervention in pathologies associated with nGPCR-x normal and aberrant biological activity.

The invention includes several assay systems for identifying nGPCR-x binding partners. In solution assays, methods of the invention comprise the steps of (a) contacting a nGPCR-x polypeptide with one or more candidate binding partner compounds and (b) identifying the compounds that bind to the nGPCR-x polypeptide. Identification of the compounds that bind the nGPCR-x polypeptide can be achieved by isolating the nGPCR-x polypeptide/binding partner complex, and separating the binding partner compound from the nGPCR-x polypeptide. An additional step of characterizing the physical, biological, and/or biochemical properties of the binding partner compound is also comprehended in another embodiment of the invention, wherein compounds identified as binding nGPCR-x may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x. In one aspect, the nGPCR-x polypeptide/binding partner complex is isolated using an antibody immunospecific for either the nGPCR-x polypeptide or the candidate binding partner compound.

In still other embodiments, either the nGPCR-x polypeptide or the candidate binding partner compound comprises a label or tag that facilitates its isolation, and methods of the invention to identify binding partner compounds include a step of isolating the nGPCR-x polypeptide/binding partner complex through interaction with the label or tag. An exemplary tag of this type is a poly-histidine sequence, generally around six histidine residues, that permits isolation of a compound so labeled using nickel chelation.

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Other labels and tags, such as the FLAG® tag (Eastman Kodak, Rochester, NY), well known and routinely used in the art, are embraced by the invention.

In one variation of an *in vitro* assay, the invention provides a method comprising the steps of (a) contacting an immobilized nGPCR-x polypeptide with a candidate binding partner compound and (b) detecting binding of the candidate compound to the nGPCR-x polypeptide. In an alternative embodiment, the candidate binding partner compound is immobilized and binding of nGPCR-x is detected. Immobilization is accomplished using any of the methods well known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interactions such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

The invention also provides cell-based assays to identify binding partner compounds of a nGPCR-x polypeptide. In one embodiment, the invention provides a method comprising the steps of contacting a nGPCR-x polypeptide expressed on the surface of a cell with a candidate binding partner compound and detecting binding of the candidate binding partner compound to the nGPCR-x polypeptide. In a preferred embodiment, the detection comprises detecting a calcium flux or other physiological event in the cell caused by the binding of the molecule.

Another aspect of the present invention is directed to methods of identifying compounds that bind to either nGPCR-x or nucleic acid molecules encoding nGPCR-x, comprising contacting nGPCR-x, or a nucleic acid molecule encoding the same, with a compound, and determining whether the compound binds nGPCR-x or a nucleic acid molecule encoding the same. Binding can be determined by binding assays which are well known to the skilled artisan, including, but not limited to, gel-shift assays, Western blots, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis,

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southwestern analysis, ELISA, and the like, which are described in, for example, *Current Protocols in Molecular Biology*, **1999**, John Wiley & Sons, NY, which is incorporated herein by reference in its entirety. The compounds to be screened include (which may include compounds which are suspected to bind nGPCR-x, or a nucleic acid molecule encoding the same), but are not limited to, extracellular, intracellular, biologic or chemical origin. The methods of the invention also embrace ligands, especially neuropeptides, that are attached to a label, such as a radiolabel (*e.g.*, ^{125}I, ^{35}S, ^{32}P, ^{33}P, ^{3}H), a fluorescence label, a chemiluminescent label, an enzymic label and an immunogenic label. Modulators falling within the scope of the invention include, but are not limited to, non-peptide molecules such as non-peptide mimetics, non-peptide allosteric effectors, and peptides. The nGPCR-x polypeptide or polynucleotide employed in such a test may either be free in solution, attached to a solid support, borne on a cell surface or located intracellularly or associated with a portion of a cell. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

In another embodiment of the invention, high throughput screening for compounds having suitable binding affinity to nGPCR-x is employed. Briefly, large numbers of different test compounds are synthesized on a solid substrate. The peptide test compounds are contacted with nGPCR-x and washed. Bound nGPCR-x is then detected by methods well known in the art. Purified polypeptides of the invention can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the protein and immobilize it on the solid support.

Generally, an expressed nGPCR-x can be used for HTS binding assays in conjunction with its defined ligand, in this case the corresponding neuropeptide that activates it. The identified peptide is labeled with a suitable radioisotope, including, but not limited to, ^{125}I, ^{3}H, ^{35}S or ^{32}P, by methods that are well known to those skilled in the art. Alternatively, the peptides may be labeled by well-known methods with a suitable fluorescent derivative (Baindur *et al.*, *Drug Dev. Res.*, **1994**, *33*, 373-398; Rogers, *Drug Discovery Today*, **1997**, *2*, 156-160). Radioactive ligand specifically bound to the receptor

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in membrane preparations made from the cell line expressing the recombinant protein can be detected in HTS assays in one of several standard ways, including filtration of the receptor-ligand complex to separate bound ligand from unbound ligand (Williams, *Med. Res. Rev.*, **1991**, *11*, 147-184; Sweetnam *et al.*, *J. Natural Products*, **1993**, *56*, 441-455). Alternative methods include a scintillation proximity assay (SPA) or a FlashPlate format in which such separation is unnecessary (Nakayama, *Cur. Opinion Drug Disc. Dev.*, **1998**, *1*, 85-91 Bossé *et al.*, *J. Biomolecular Screening*, **1998**, *3*, 285-292.). Binding of fluorescent ligands can be detected in various ways, including fluorescence energy transfer (FRET), direct spectrophotofluorometric analysis of bound ligand, or fluorescence polarization (Rogers, *Drug Discovery Today*, **1997**, *2*, 156-160; Hill, *Cur. Opinion Drug Disc. Dev.*, **1998**, *1*, 92-97).

Other assays may be used to identify specific ligands of a nGPCR-x receptor, including assays that identify ligands of the target protein through measuring direct binding of test ligands to the target protein, as well as assays that identify ligands of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two-hybrid system described in Fields *et al.*, Nature, 340:245-246 (1989), and Fields *et al.*, Trends in Genetics, 10:286-292 (1994), both of which are incorporated herein by reference. The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this methodology have been developed to clone genes that encode DNA binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of interacting proteins to bring a transcription activation domain into close proximity with a DNA binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the

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reporter gene. The second hybrid protein, which contains the activation domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. For example, when the first protein is a GPCR gene product, or fragment thereof, that is known to interact with another protein or nucleic acid, this assay can be used to detect agents that interfere with the binding interaction. Expression of the reporter gene is monitored as different test agents are added to the system. The presence of an inhibitory agent results in lack of a reporter signal.

The yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to a nGPCR-x receptor, or fragment thereof, a fusion polynucleotide encoding both a nGPCR-x receptor (or fragment) and a UAS binding domain (*i.e.*, a first protein) may be used. In addition, a large number of hybrid genes each encoding a different second protein fused to an activation domain are produced and screened in the assay. Typically, the second protein is encoded by one or more members of a total cDNA or genomic DNA fusion library, with each second protein-coding region being fused to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein is described in U.S. Patent No. 5,585,277, incorporated herein by reference. This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (*i.e.*, when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target

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protein can be determined by any method that distinguishes between the folded and unfolded states of the target protein. The function of the target protein need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

Another method for identifying ligands of a target protein is described in Wieboldt *et al.*, Anal. Chem., 69:1683-1691 (1997), incorporated herein by reference. This technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding to the target protein. Agents that bind to the target protein are separated from other library components by simple membrane washing. The specifically selected molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

Other embodiments of the invention comprise using competitive screening assays in which neutralizing antibodies capable of binding a polypeptide of the invention specifically compete with a test compound for binding to the polypeptide. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with nGPCR-x. Radiolabeled competitive binding studies are described in A.H. Lin *et al. Antimicrobial Agents and Chemotherapy*, **1997**, vol. 41, no. 10. pp. 2127-2131, the disclosure of which is incorporated herein by reference in its entirety.

Identification of modulating agents

The invention also provides methods for identifying a modulator of binding between a nGPCR-x and a nGPCR-x binding partner, comprising the steps of: (a) contacting a nGPCR-x binding partner and a composition comprising a nGPCR-x in the presence and in the absence of a putative modulator compound; (b) detecting binding between the binding partner and the nGPCR-x; and (c) identifying a putative modulator compound or a modulator compound in view of decreased or increased binding between the binding partner and the nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator. Following steps (a) and (b),

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compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate modulation of binding to nGPCR-x.

nGPCR-x binding partners that stimulate nGPCR-x activity are useful as agonists in disease states or conditions characterized by insufficient nGPCR-x signaling (*e.g.*, as a result of insufficient activity of a nGPCR-x ligand). nGPCR-x binding partners that block ligand-mediated nGPCR-x signaling are useful as nGPCR-x antagonists to treat disease states or conditions characterized by excessive nGPCR-x signaling. In addition nGPCR-x modulators in general, as well as nGPCR-x polynucleotides and polypeptides, are useful in diagnostic assays for such diseases or conditions.

In another aspect, the invention provides methods for treating a disease or abnormal condition by administering to a patient in need of such treatment a substance that modulates the activity or expression of a polypeptide having sequences selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240.

Agents that modulate (*i.e.*, increase, decrease, or block) nGPCR-x activity or expression may be identified by incubating a putative modulator with a cell containing a nGPCR-x polypeptide or polynucleotide and determining the effect of the putative modulator on nGPCR-x activity or expression. The selectivity of a compound that modulates the activity of nGPCR-x can be evaluated by comparing its effects on nGPCR-x to its effect on other GPCR compounds. Following identification of compounds that modulate nGPCR-x activity or expression, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Selective modulators may include, for example, antibodies and other proteins, peptides, or organic molecules that specifically bind to a nGPCR-x polypeptide or a nGPCR-x-encoding nucleic acid. Modulators of nGPCR-x activity will be therapeutically useful in treatment of diseases and physiological conditions in which normal or aberrant nGPCR-x activity is involved. nGPCR-x polynucleotides, polypeptides, and modulators may be used in the treatment of such diseases and conditions as infections, such as viral infections caused by HIV-1 or HIV-2; pain; cancers; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction,

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cardiomyopathies, atherosclerosis, *etc.*); Parkinson's disease; and psychotic and neurological disorders, including schizophrenia, migraine, ADHH, major depression, anxiety, mental disorder, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Tourette's Syndrome, among others. nGPCR-x polynucleotides and polypeptides, as well as nGPCR-x modulators, may also be used in diagnostic assays for such diseases or conditions.

Methods of the invention to identify modulators include variations on any of the methods described above to identify binding partner compounds, the variations including techniques wherein a binding partner compound has been identified and the binding assay is carried out in the presence and absence of a candidate modulator. A modulator is identified in those instances where binding between the nGPCR-x polypeptide and the binding partner compound changes in the presence of the candidate modulator compared to binding in the absence of the candidate modulator compound. A modulator that increases binding between the nGPCR-x polypeptide and the binding partner compound is described as an enhancer or activator, and a modulator that decreases binding between the nGPCR-x polypeptide and the binding partner compound is described as an inhibitor. Following identification of modulators, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

The invention also comprehends high-throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity (*i.e.*, affect enzymatic activity, binding activity, *etc.*) of a nGPCR-x polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate nGPCR-x receptor-ligand interaction. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable structure/activity relationship between the "hit" and the nGPCR-x polypeptide.

Another aspect of the present invention is directed to methods of identifying compounds which modulate (*i.e.*, increase or decrease) an activity of nGPCR-x comprising contacting nGPCR-x with a compound, and determining whether the

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compound modifies activity of nGPCR-x. The activity in the presence of the test compared is measured to the activity in the absence of the test compound. Where the activity of the sample containing the test compound is higher than the activity in the sample lacking the test compound, the compound will have increased activity. Similarly, where the activity of the sample containing the test compound is lower than the activity in the sample lacking the test compound, the compound will have inhibited activity. Following the identification of compounds that modulate an activity of nGPCR-x, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

The present invention is particularly useful for screening compounds by using nGPCR-x in any of a variety of drug screening techniques. The compounds to be screened include (which may include compounds which are suspected to modulate nGPCR-x activity), but are not limited to, extracellular, intracellular, biologic or chemical origin. The nGPCR-x polypeptide employed in such a test may be in any form, preferably, free in solution, attached to a solid support, borne on a cell surface or located intracellularly. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

The activity of nGPCR-x polypeptides of the invention can be determined by, for example, examining the ability to bind or be activated by chemically synthesized peptide ligands. Alternatively, the activity of nGPCR-x polypeptides can be assayed by examining their ability to bind calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and photons. Alternatively, the activity of the nGPCR-x polypeptides can be determined by examining the activity of effector molecules including, but not limited to, adenylate cyclase, phospholipases and ion channels. Thus, modulators of nGPCR-x polypeptide activity may alter a GPCR receptor function, such as a binding property of a receptor or an activity such as G protein-mediated signal transduction or membrane localization. In various embodiments of the method, the assay may take the form of an ion flux assay, a yeast growth assay, a non-hydrolyzable GTP assay such as a [^{35}S]-GTP γS assay, a cAMP assay, an inositol

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triphosphate assay, a diacylglycerol assay, an Aequorin assay, a Luciferase assay, a FLIPR assay for intracellular Ca^{2+} concentration, a mitogenesis assay, a MAP Kinase activity assay, an arachidonic acid release assay (*e.g.*, using [^{3}H]-arachidonic acid), and an assay for extracellular acidification rates, as well as other binding or function-based assays of nGPCR-x activity that are generally known in the art. In several of these embodiments, the invention comprehends the inclusion of any of the G proteins known in the art, such as G_{16}, G_{15}, or chimeric G_{qd5}, G_{qs5}, G_{qo5}, G_{q25}, and the like. nGPCR-x activity can be determined by methodologies that are used to assay for FaRP activity, which is well known to those skilled in the art. Biological activities of nGPCR-x receptors according to the invention include, but are not limited to, the binding of a natural or an unnatural ligand, as well as any one of the functional activities of GPCRs known in the art. Non-limiting examples of GPCR activities include transmembrane signaling of various forms, which may involve G protein association and/or the exertion of an influence over G protein binding of various guanidylate nucleotides; another exemplary activity of GPCRs is the binding of accessory proteins or polypeptides that differ from known G proteins.

The modulators of the invention exhibit a variety of chemical structures, which can be generally grouped into non-peptide mimetics of natural GPCR receptor ligands, peptide and non-peptide allosteric effectors of GPCR receptors, and peptides that may function as activators or inhibitors (competitive, uncompetitive and non-competitive) (*e.g.*, antibody products) of GPCR receptors. The invention does not restrict the sources for suitable modulators, which may be obtained from natural sources such as plant, animal or mineral extracts, or non-natural sources such as small molecule libraries, including the products of combinatorial chemical approaches to library construction, and peptide libraries. Examples of peptide modulators of GPCR receptors exhibit the following primary structures: GLGPRPLRFamide, GNSFLRFamide, GGPQGPLRFamide, GPSGPLRFamide, PDVDHVFLRFamide, and pyro-EDVDHVFLRFamide.

Other assays can be used to examine enzymatic activity including, but not limited to, photometric, radiometric, HPLC, electrochemical, and the like, which are described in, for example, *Enzyme Assays: A Practical Approach*, eds. R. Eisenthal and M. J. Danson, 1992, Oxford University Press, which is incorporated herein by reference in its entirety.

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The use of cDNAs encoding GPCRs in drug discovery programs is well-known; assays capable of testing thousands of unknown compounds per day in high-throughput screens (HTSs) are thoroughly documented. The literature is replete with examples of the use of radiolabeled ligands in HTS binding assays for drug discovery (see Williams, *Medicinal Research Reviews*, **1991**, *11*, 147-184.; Sweetnam, *et al.*, *J. Natural Products*, **1993**, *56*, 441-455 for review). Recombinant receptors are preferred for binding assay HTS because they allow for better specificity (higher relative purity), provide the ability to generate large amounts of receptor material, and can be used in a broad variety of formats (see Hodgson, *Bio/Technology*, **1992**, *10*, 973-980; each of which is incorporated herein by reference in its entirety).

A variety of heterologous systems is available for functional expression of recombinant receptors that are well known to those skilled in the art. Such systems include bacteria (Strosberg, *et al.*, *Trends in Pharmacological Sciences*, **1992**, *13*, 95-98), yeast (Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494), several kinds of insect cells (Vanden Broeck, *Int. Rev. Cytology*, **1996**, *164*, 189-268), amphibian cells (Jayawickreme *et al.*, *Current Opinion in Biotechnology*, **1997**, *8*, 629-634) and several mammalian cell lines (CHO, HEK-293, COS, etc.; see Gerhardt, *et al.*, *Eur. J. Pharmacology*, **1997**, *334*, 1-23). These examples do not preclude the use of other possible cell expression systems, including cell lines obtained from nematodes (PCT application WO 98/37177).

In preferred embodiments of the invention, methods of screening for compounds that modulate nGPCR-x activity comprise contacting test compounds with nGPCR-x and assaying for the presence of a complex between the compound and nGPCR-x. In such assays, the ligand is typically labeled. After suitable incubation, free ligand is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular compound to bind to nGPCR-x.

It is well known that activation of heterologous receptors expressed in recombinant systems results in a variety of biological responses, which are mediated by G proteins expressed in the host cells. Occupation of a GPCR by an agonist results in exchange of bound GDP for GTP at a binding site on the G_α subunit; one can use a radioactive, non-hydrolyzable derivative of GTP, GTPγ[^{35}S], to measure binding of an agonist to the receptor (Sim *et al.*, Neuroreport, **1996**, *7*, 729-733). One can also use this binding to

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measure the ability of antagonists to bind to the receptor by decreasing binding of GTPγ[^{35}S] in the presence of a known agonist. One could therefore construct a HTS based on GTPγ[^{35}S] binding, though this is not the preferred method.

The G proteins required for functional expression of heterologous GPCRs can be native constituents of the host cell or can be introduced through well-known recombinant technology. The G proteins can be intact or chimeric. Often, a nearly universally competent G protein (e.g., $G_{\alpha 16}$) is used to couple any given receptor to a detectable response pathway. G protein activation results in the stimulation or inhibition of other native proteins, events that can be linked to a measurable response.

Examples of such biological responses include, but are not limited to, the following: the ability to survive in the absence of a limiting nutrient in specifically engineered yeast cells (Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494); changes in intracellular Ca^{2+} concentration as measured by fluorescent dyes (Murphy, *et al.*, *Cur. Opinion Drug Disc. Dev.*, **1998**, *1*, 192-199). Fluorescence changes can also be used to monitor ligand-induced changes in membrane potential or intracellular pH; an automated system suitable for HTS has been described for these purposes (Schroeder, *et al.*, *J. Biomolecular Screening*, **1996**, *1*, 75-80). Melanophores prepared from *Xenopus laevis* show a ligand-dependent change in pigment organization in response to heterologous GPCR activation; this response is adaptable to HTS formats (Jayawickreme *et al.*, *Cur. Opinion Biotechnology*, **1997**, *8*, 629-634). Assays are also available for the measurement of common second messengers, including cAMP, phosphoinositides and arachidonic acid, but these are not generally preferred for HTS.

Preferred methods of HTS employing these receptors include permanently transfected CHO cells, in which agonists and antagonists can be identified by the ability to specifically alter the binding of GTPγ[^{35}S] in membranes prepared from these cells. In another embodiment of the invention, permanently transfected CHO cells could be used for the preparation of membranes which contain significant amounts of the recombinant receptor proteins; these membrane preparations would then be used in receptor binding assays, employing the radiolabeled ligand specific for the particular receptor. Alternatively, a functional assay, such as fluorescent monitoring of ligand-induced changes in internal Ca^{2+} concentration or membrane potential in permanently transfected

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CHO cells containing each of these receptors individually or in combination would be preferred for HTS. Equally preferred would be an alternative type of mammalian cell, such as HEK-293 or COS cells, in similar formats. More preferred would be permanently transfected insect cell lines, such as *Drosophila* S2 cells. Even more preferred would be recombinant yeast cells expressing the *Drosophila melanogaster* receptors in HTS formats well known to those skilled in the art (*e.g.*, Pausch, *Trends in Biotechnology*, **1997**, *15*, 487-494).

The invention contemplates a multitude of assays to screen and identify inhibitors of ligand binding to nGPCR-x receptors. In one example, the nGPCR-x receptor is immobilized and interaction with a binding partner is assessed in the presence and absence of a candidate modulator such as an inhibitor compound. In another example, interaction between the nGPCR-x receptor and its binding partner is assessed in a solution assay, both in the presence and absence of a candidate inhibitor compound. In either assay, an inhibitor is identified as a compound that decreases binding between the nGPCR-x receptor and its binding partner. Following the identification of compounds which inhibit ligand binding to nGPCR-x receptors, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Another contemplated assay involves a variation of the dihybrid assay wherein an inhibitor of protein/protein interactions is identified by detection of a positive signal in a transformed or transfected host cell, as described in PCT publication number WO 95/20652, published August 3, 1995.

Candidate modulators contemplated by the invention include compounds selected from libraries of either potential activators or potential inhibitors. There are a number of different libraries used for the identification of small molecule modulators, including: (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules. Chemical libraries consist of random chemical structures, some of which are analogs of known compounds or analogs of compounds that have been identified as "hits" or "leads" in other drug discovery screens, some of which are derived from natural products, and some of which arise from non-directed synthetic organic chemistry. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures

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for screening by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) thereof. For a review, see Science 282:63-68 (1998). Combinatorial libraries are composed of large numbers of peptides, oligonucleotides, or organic compounds as a mixture. These libraries are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning, or proprietary synthetic methods. Of particular interest are non-peptide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as such binding partners as chimeric, or fusion, proteins. A "binding partner" as used herein broadly encompasses non-peptide modulators, as well as such peptide modulators as neuropeptides other than natural ligands, antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified nGPCR-x gene.

The polypeptides of the invention are employed as a research tool for identification, characterization and purification of interacting, regulatory proteins. Appropriate labels are incorporated into the polypeptides of the invention by various methods known in the art and the polypeptides are used to capture interacting molecules. For example, molecules are incubated with the labeled polypeptides, washed to remove unbound polypeptides, and the polypeptide complex is quantified. Data obtained using different concentrations of polypeptide are used to calculate values for the number, affinity, and association of polypeptide with the protein complex.

Labeled polypeptides are also useful as reagents for the purification of molecules with which the polypeptide interacts including, but not limited to, inhibitors. In one embodiment of affinity purification, a polypeptide is covalently coupled to a

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chromatography column. Cells and their membranes are extracted, and various cellular subcomponents are passed over the column. Molecules bind to the column by virtue of their affinity to the polypeptide. The polypeptide-complex is recovered from the column, dissociated and the recovered molecule is subjected to protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotides for cloning the corresponding gene from an appropriate cDNA library.

Alternatively, compounds may be identified which exhibit similar properties to the ligand for the nGPCR-x of the invention, but which are smaller and exhibit a longer half time than the endogenous ligand in a human or animal body. When an organic compound is designed, a molecule according to the invention is used as a "lead" compound. The design of mimetics to known pharmaceutically active compounds is a well-known approach in the development of pharmaceuticals based on such "lead" compounds. Mimetic design, synthesis and testing are generally used to avoid randomly screening a large number of molecules for a target property. Furthermore, structural data deriving from the analysis of the deduced amino acid sequences encoded by the DNAs of the present invention are useful to design new drugs, more specific and therefore with a higher pharmacological potency.

Comparison of the protein sequence of the present invention with the sequences present in all the available databases showed a significant homology with the transmembrane portion of G protein coupled receptors. Accordingly, computer modeling can be used to develop a putative tertiary structure of the proteins of the invention based on the available information of the transmembrane domain of other proteins. Thus, novel ligands based on the predicted structure of nGPCR-x can be designed.

In a particular embodiment, the novel molecules identified by the screening methods according to the invention are low molecular weight organic molecules, in which case a composition or pharmaceutical composition can be prepared thereof for oral intake, such as in tablets. The compositions, or pharmaceutical compositions, comprising the nucleic acid molecules, vectors, polypeptides, antibodies and compounds identified by the screening methods described herein, can be prepared for any route of administration including, but not limited to, oral, intravenous, cutaneous, subcutaneous, nasal, intramuscular or intraperitoneal. The nature of the carrier or other ingredients will depend

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on the specific route of administration and particular embodiment of the invention to be administered. Examples of techniques and protocols that are useful in this context are, *inter alia*, found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A (ed.), 1980, which is incorporated herein by reference in its entirety.

The dosage of these low molecular weight compounds will depend on the disease state or condition to be treated and other clinical factors such as weight and condition of the human or animal and the route of administration of the compound. For treating human or animals, between approximately 0.5 mg/kg of body weight to 500 mg/kg of body weight of the compound can be administered. Therapy is typically administered at lower dosages and is continued until the desired therapeutic outcome is observed.

The present compounds and methods, including nucleic acid molecules, polypeptides, antibodies, compounds identified by the screening methods described herein, have a variety of pharmaceutical applications and may be used, for example, to treat or prevent unregulated cellular growth, such as cancer cell and tumor growth. In a particular embodiment, the present molecules are used in gene therapy. For a review of gene therapy procedures, see *e.g.* Anderson, *Science*, **1992**, *256*, 808-813, which is incorporated herein by reference in its entirety.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing a nGPCR-x natural binding partner associated activity in a mammal comprising administering to said mammal an agonist or antagonist to one of the above disclosed polypeptides in an amount sufficient to effect said agonism or antagonism. One embodiment of the present invention, then, is a method of treating diseases in a mammal with an agonist or antagonist of the protein of the present invention comprises administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize nGPCR-x-associated functions.

In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that modulate the function of G protein coupled receptors. Some small organic molecules form a class of compounds that modulate the function of G protein coupled receptors.

Exemplary diseases and conditions amenable to treatment based on the present invention include, but are not limited to, thyroid disorders (*e.g.* thyreotoxicosis,

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myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in U.S. Application Serial No. 08/702,282, filed August 23, 1996 and International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used and the size and physiological condition of the patient. Therapeutically effective doses for the compounds described herein can be estimated initially from cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the IC_{50} as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.

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Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors and major organs can also be determined to facilitate the selection of drugs most appropriate to inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.

Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.

At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, Journal of American Veterinary Medical Assoc., 202:229-249, 1993). Representative animals from each treatment group can then be examined by gross necropsy for immediate evidence of metastasis, unusual illness or toxicity. Gross abnormalities in tissue are noted and tissues are examined histologically. Compounds causing a reduction in body weight or blood components are less preferred, as are compounds having an adverse effect on major organs. In general, the greater the adverse effect the less preferred the compound.

For the treatment of many diseases, the expected daily dose of a hydrophobic pharmaceutical agent is between 1 to 500 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to 50 mg/day. Drugs can be delivered less frequently provided plasma levels of the active moiety are sufficient to maintain therapeutic effectiveness. Plasma levels

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should reflect the potency of the drug. Generally, the more potent the compound the lower the plasma levels necessary to achieve efficacy.

As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. nGPCR-x mRNA transcripts may found in many other tissues, including, but not limited to peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

Sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 will, as detailed above, enable screening the endogenous neurotransmitters/hormones/ligands which activate, agonize, or antagonize nGPCR-x and for compounds with potential utility in treating disorders including, but not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including schizophrenia, migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

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For example, nGPCR-x may be useful in the treatment of respiratory ailments such as asthma, where T cells are implicated by the disease. Contraction of airway smooth muscle is stimulated by thrombin. Cicala *et al* (1999) Br J Pharmacol 126:478-484. Additionally, in bronchiolitis obliterans, it has been noted that activation of thrombin receptors may be deleterious. Hauck *et al.* (1999) Am J Physiol 277:L22-L29. Furthermore, mast cells have also been shown to have thrombin receptors. Cirino *et al* (1996) J Exp Med 183:821-827. nGPCR-x may also be useful in remodeling of airway structure s in chronic pulmonary inflammation via stimulation of fibroblast procollagen synthesis. See, e.g., Chambers *et al.* (1998) Biochem J 333:121-127; Trejo *et al.* (1996) J Biol Chem 271:21536-21541.

In another example, increased release of sCD40L and expression of CD40L by T cells after activation of thrombin receptors suggests that nGPCR-x may be useful in the treatment of unstable angina due to the role of T cells and inflammation. See Aukrust *et al.* (1999) Circulation 100:614-620.

A further example is the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and thyroiditis. Due to the tissue expression profile of nGPCR-x, inhibition of thrombin receptors may be beneficial for these diseases. See, *e.g.*, Morris *et al.* (1996) Ann Rheum Dis 55:841-843. In addition to T cells, NK cells and monocytes are also critical cell types which contribute to the pathogenesis of these diseases. See, e.g., Naldini & Carney (1996) Cell Immunol 172:35-42; Hoffman & Cooper (1995) Blood Cells Mol Dis 21:156-167; Colotta *et al.* (1994) Am J Pathol 144:975-985.

Expression of nGPCR-x in bone marrow and spleen may suggest that it may play a role in the proliferation of hematopoietic progenitor cells. See DiCuccio *et al.* (1996) Exp Hematol 24:914-918.

As another example, nGPCR-x may be useful in the treatment of acute and/or traumatic brain injury. Astrocytes have been demonstrated to express thrombin receptors. Activation of thrombin receptors may be involved in astrogliosis following brain injury. Therefore, inhibition of receptor activity may be beneficial for limiting neuroinflammation. Scar formation mediated by astrocytes may also be limited by inhibiting thrombin receptors. See, *e.g*, Pindon *et al.* (1998) Eur J Biochem 255:766-774;

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Ubl & Reiser. (1997) Glia 21:361-369; Grabham & Cunningham (1995) J Neurochem 64:583-591.

nGPCR-x receptor activation may mediate neuronal and astrocyte apoptosis and prevention of neurite outgrowth. Inhibition would be beneficial in both chronic and acute brain injury. See, *e.g.*, Donovan *et al.* (1997) J Neurosci 17:5316-5326; Turgeon *et al* (1998) J Neurosci 18:6882-6891; Smith-Swintosky *et al.* (1997) J Neurochem 69:1890-1896; Gill *et al.* (1998) Brain Res 797:321-327; Suidan *et al.* (1996) Semin Thromb Hemost 22:125-133.

The attached Sequence Listing contains the sequences of the polynucleotides and polypeptides of the invention and is incorporated herein by reference in its entirety.

Methods of Screening Human Subjects

Thus in yet another embodiment, the invention provides genetic screening procedures that entail analyzing a person's genome -- in particular their alleles for the nGPCR-x of the invention -- to determine whether the individual possesses a genetic characteristic found in other individuals that are considered to be afflicted with, or at risk for, developing a mental disorder or disease of the brain that is suspected of having a hereditary component. For example, in one embodiment, the invention provides a method for determining a potential for developing a disorder affecting the brain in a human subject comprising the steps of analyzing the coding sequence of one or more nGPCR-x genes from the human subject; and determining development potential for the disorder in said human subject from the analyzing step.

More particularly, the invention provides a method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of: (a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the amino acid sequence, expression, or biological activity of at least one seven transmembrane receptor that is expressed in the brain, wherein the seven transmembrane receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120, or an allelic variant thereof, and wherein the nucleic acid corresponds to the gene encoding the seven transmembrane receptor; and (b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence,

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expression, or biological activity of allele in the nucleic acid correlates with an increased risk of developing the disorder.

By "human subject" is meant any human being, human embryo, or human fetus. It will be apparent that methods of the present invention will be of particular interest to individuals that have themselves been diagnosed with a disorder affecting the brain or have relatives that have been diagnosed with a disorder affecting the brain.

By "screening for an increased risk" is meant determination of whether a genetic variation exists in the human subject that correlates with a greater likelihood of developing a disorder affecting the brain than exists for the human population as a whole, or for a relevant racial or ethnic human sub-population to which the individual belongs. Both positive and negative determinations (i.e., determinations that a genetic predisposition marker is present or is absent) are intended to fall within the scope of screening methods of the invention. In preferred embodiments, the presence of a mutation altering the sequence or expression of at least one nGPCR-x seven transmembrane receptor allele in the nucleic acid is correlated with an increased risk of developing mental disorder, whereas the absence of such a mutation is reported as a negative determination.

The "assaying" step of the invention may involve any techniques available for analyzing nucleic acid to determine its characteristics, including but not limited to well-known techniques such as single-strand conformation polymorphism analysis (SSCP) [Orita *et al., Proc Natl. Acad. Sci. USA, 86*: 2766-2770 (1989)]; heteroduplex analysis [White *et al., Genomics, 12*: 301-306 (1992)]; denaturing gradient gel electrophoresis analysis [Fischer *et al., Proc. Natl. Acad. Sci. USA, 80*: 1579-1583 (1983); and Riesner *et al., Electrophoresis, 10*: 377-389 (1989)]; DNA sequencing; RNase cleavage [Myers *et al., Science, 230*: 1242-1246 (1985)]; chemical cleavage of mismatch techniques [Rowley *et al., Genomics, 30*: 574-582 (1995); and Roberts *et al., Nucl. Acids Res., 25*: 3377-3378 (1997)]; restriction fragment length polymorphism analysis; single nucleotide primer extension analysis [Shumaker *et al., Hum. Mutat., 7*: 346-354 (1996); and Pastinen *et al., Genome Res., 7*: 606-614 (1997)]; 5' nuclease assays [Pease *et al., Proc. Natl. Acad. Sci. USA, 91*:5022-5026 (1994)]; DNA Microchip analysis [Ramsay, G., *Nature Biotechnology, 16*: 40-48 (1999); and Chee *et al.*, U.S. Patent No. 5,837,832]; and ligase chain reaction [Whiteley *et al.*, U.S. Patent No. 5,521,065]. [See generally, Schafer and

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Hawkins, *Nature Biotechnology, 16*: 33-39 (1998).] All of the foregoing documents are hereby incorporated by reference in their entirety.

Thus, in one preferred embodiment involving screening nGPCR-x sequences, for example, the assaying step comprises at least one procedure selected from the group consisting of: (a) determining a nucleotide sequence of at least one codon of at least one nGPCR-x allele of the human subject; (b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; (c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and (d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

In a highly preferred embodiment, the assaying involves sequencing of nucleic acid to determine nucleotide sequence thereof, using any available sequencing technique. [See, *e.g.*, Sanger *et al., Proc. Natl. Acad. Sci. (USA), 74*: 5463-5467 (1977) (dideoxy chain termination method); Mirzabekov, *TIBTECH, 12*: 27-32 (1994) (sequencing by hybridization); Drmanac *et al., Nature Biotechnology, 16*: 54-58 (1998); U.S. Patent No. 5,202,231; and *Science, 260*: 1649-1652 (1993) (sequencing by hybridization); Kieleczawa *et al., Science, 258*: 1787-1791 (1992) (sequencing by primer walking); (Douglas *et al., Biotechniques, 14*: 824-828 (1993) (Direct sequencing of PCR products); and Akane *et al., Biotechniques 16*: 238-241 (1994); Maxam and Gilbert, *Meth. Enzymol., 65*: 499-560 (1977) (chemical termination sequencing), all incorporated herein by reference.] The analysis may entail sequencing of the entire nGPCR gene genomic DNA sequence, or portions thereof; or sequencing of the entire seven transmembrane receptor coding sequence or portions thereof. In some circumstances, the analysis may involve a determination of whether an individual possesses a particular allelic variant, in which case sequencing of only a small portion of nucleic acid -- enough to determine the sequence of a particular codon characterizing the allelic variant -- is sufficient. This approach is appropriate, for example, when assaying to determine whether one family member inherited the same allelic variant that has been previously characterized for another family

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member, or, more generally, whether a person's genome contains an allelic variant that has been previously characterized and correlated with a mental disorder having a heritable component.

In another highly preferred embodiment, the assaying step comprises performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences. In a preferred embodiment, the hybridization involves a determination of whether nucleic acid derived from the human subject will hybridize with one or more oligonucleotides, wherein the oligonucleotides have nucleotide sequences that correspond identically to a portion of the nGPCR-x gene sequence taught herein, or that correspond identically except for one mismatch. The hybridization conditions are selected to differentiate between perfect sequence complementarity and imperfect matches differing by one or more bases. Such hybridization experiments thereby can provide single nucleotide polymorphism sequence information about the nucleic acid from the human subject, by virtue of knowing the sequences of the oligonucleotides used in the experiments.

Several of the techniques outlined above involve an analysis wherein one performs a polynucleotide migration assay, *e.g.*, on a polyacrylamide electrophoresis gel (or in a capillary electrophoresis system), under denaturing or non-denaturing conditions. Nucleic acid derived from the human subject is subjected to gel electrophoresis, usually adjacent to (or co-loaded with) one or more reference nucleic acids, such as reference GPCR-x encoding sequences having a coding sequence identical to all or a portion of SEQ ID NOS: 1 to 120 (or identical except for one known polymorphism). The nucleic acid from the human subject and the reference sequence(s) are subjected to similar chemical or enzymatic treatments and then electrophoresed under conditions whereby the polynucleotides will show a differential migration pattern, unless they contain identical sequences. [See generally Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, New York: John Wiley & Sons, Inc. (1987-1999); and Sambrook *et al.*, (eds.), Molecular Cloning, *A Laboratory Manual*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1989), both incorporated herein by reference in their entirety.]

In the context of assaying, the term "nucleic acid of a human subject" is intended to include nucleic acid obtained directly from the human subject (*e.g.*, DNA or RNA

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obtained from a biological sample such as a blood, tissue, or other cell or fluid sample); and also nucleic acid derived from nucleic acid obtained directly from the human subject. By way of non-limiting examples, well known procedures exist for creating cDNA that is complementary to RNA derived from a biological sample from a human subject, and for amplifying (*e.g.*, via polymerase chain reaction (PCR)) DNA or RNA derived from a biological sample obtained from a human subject. Any such derived polynucleotide which retains relevant nucleotide sequence information of the human subject's own DNA/RNA is intended to fall within the definition of "nucleic acid of a human subject" for the purposes of the present invention.

In the context of assaying, the term "mutation" includes addition, deletion, and/or substitution of one or more nucleotides in the GPCR gene sequence (*e.g.*, as compared to the seven transmembrane receptor-encoding sequences set forth of SEQ ID NO:1 to SEQ ID NO:120, and other polymorphisms that occur in introns (where introns exist) and that are identifiable via sequencing, restriction fragment length polymorphism, or other techniques. The various activity examples provided herein permit determination of whether a mutation modulates activity of the relevant receptor in the presence or absence of various test substances.

In a related embodiment, the invention provides methods of screening a person's genotype with respect to the nGPCR-x of the invention, and correlating such genotypes with diagnoses for disease or with predisposition for disease (for genetic counseling). For example, the invention provides a method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of: (a) providing a biological sample comprising nucleic acid from the patient, the nucleic acid including sequences corresponding to said patient's nGPCR-x alleles; (b) analyzing the nucleic acid for the presence of a mutation or mutations; (c) determining a nGPCR-x genotype from the analyzing step; and (d) correlating the presence of a mutation in an nGPCR-x allele with a hereditary mental disorder genotype. In a preferred embodiment, the biological sample is a cell sample containing human cells that contain genomic DNA of the human subject. The analyzing can be performed analogously to the assaying described in preceding paragraphs. For example, the analyzing comprises sequencing a portion of the nucleic

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acid (e.g., DNA or RNA), the portion comprising at least one codon of the nGPCR-x alleles.

Although more time consuming and expensive than methods involving nucleic acid analysis, the invention also may be practiced by assaying one or more proteins of a human subject to determine the presence or absence of an amino acid sequence variation in GPCR protein from the human subject. Such protein analyses may be performed, *e.g.*, by fragmenting GPCR protein via chemical or enzymatic methods and sequencing the resultant peptides; or by Western analyses using an antibody having specificity for a particular allelic variant of the GPCR.

The invention also provides materials that are useful for performing methods of the invention. For example, the present invention provides oligonucleotides useful as probes in the many analyzing techniques described above. In general, such oligonucleotide probes comprise 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides that have a sequence that is identical, or exactly complementary, to a portion of a human GPCR gene sequence taught herein (or allelic variant thereof), or that is identical or exactly complementary except for one nucleotide substitution. In a preferred embodiment, the oligonucleotides have a sequence that corresponds in the foregoing manner to a human GPCR coding sequence taught herein, and in particular, the coding sequences set forth in SEQ ID NO:1 to SEQ ID NO:120. In one variation, an oligonucleotide probe of the invention is purified and isolated. In another variation, the oligonucleotide probe is labeled, *e.g.*, with a radioisotope, chromophore, or fluorophore. In yet another variation, the probe is covalently attached to a solid support. [See generally Ausubel *et al.* and Sambrook *et al.*, *supra*.]

In a related embodiment, the invention provides kits comprising reagents that are useful for practicing methods of the invention. For example, the invention provides a kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association: (a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x seven transmembrane receptor gene, the oligonucleotide comprising 6-50 nucleotides that have a sequence that is identical or exactly complementary to a portion of a human nGPCR-x gene sequence or nGPCR-x

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coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and (b) a media packaged with the oligonucleotide containing information identifying polymorphisms identifiable with the probe that correlate with mental disorder or a genetic predisposition therefor. Exemplary information-containing media include printed paper package inserts or packaging labels; and magnetic and optical storage media that are readable by computers or machines used by practitioners who perform genetic screening and counseling services. The practitioner uses the information provided in the media to correlate the results of the analysis with the oligonucleotide with a diagnosis. In a preferred variation, the oligonucleotide is labeled.

In still another embodiment, the invention provides methods of identifying those allelic variants of GPCRs of the invention that correlate with mental disorders. For example, the invention provides a method of identifying a seven transmembrane allelic variant that correlates with a mental disorder, comprising steps of: (a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny; (b) analyzing the nucleic acid for the presence of a mutation or mutations in at least one seven transmembrane receptor that is expressed in the brain, wherein the at least one seven transmembrane receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 or an allelic variant thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the at least one seven transmembrane receptor; (c) determining a genotype for the patient for the at least one seven transmembrane receptor from said analyzing step; and (d) identifying an allelic variant that correlates with the mental disorder from the determining step. To expedite this process, it may be desirable to perform linkage studies in the patients (and possibly their families) to correlate chromosomal markers with disease states. The chromosomal localization data provided herein facilitates identifying an involved nGPCR with a chromosomal marker.

The foregoing method can be performed to correlate the nGPCR-x of the invention to a number of disorders having hereditary components that are causative or that

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predispose persons to the disorder. For example, in one preferred variation, the disorder is a mental disorder.

Also contemplated as part of the invention are polynucleotides that comprise the allelic variant sequences identified by such methods, and polypeptides encoded by the allelic variant sequences, and oligonucleotide and oligopeptide fragments thereof that embody the mutations that have been identified. Such materials are useful in *in vitro* cell-free and cell-based assays for identifying lead compounds and therapeutics for treatment of the disorders. For example, the variants are used in activity assays, binding assays, and assays to screen for activity modulators described herein. In one preferred embodiment, the invention provides a purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x receptor allelic variant identified according to the methods described above; and an oligonucleotide that comprises the sequences that differentiate the allelic variant from the nGPCR-x sequences set forth in SEQ ID NO:1 to SEQ ID NO:120. The invention also provides a vector comprising the polynucleotide (preferably an expression vector); and a host cell transformed or transfected with the polynucleotide or vector. The invention also provides an isolated cell line that is expressing the allelic variant nGPCR-x polypeptide; purified cell membranes from such cells; purified polypeptide; and synthetic peptides that embody the allelic variation amino acid sequence. In one particular embodiment, the invention provides a purified polynucleotide comprising a nucleotide sequence encoding a nGPCR-x seven transmembrane receptor protein of a human that is affected with a mental disorder; wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and wherein the polynucleotide encodes a nGPCR-x amino acid sequence that differs from a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, by at least one residue.

An exemplary assay for using the allelic variants is a method for identifying a modulator of nGPCR-x biological activity, comprising the steps of: (a) contacting a cell expressing the allelic variant in the presence and in the absence of a putative modulator

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compound; (b) measuring nGPCR-x biological activity in the cell; and (c) identifying a putative modulator compound in view of decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator.

Additional features of the invention will be apparent from the following Examples. Examples 1 and 2 are actual while the remaining Examples are prophetic. Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, including the detailed description, and all such features are intended as aspects of the invention. Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

EXAMPLES

EXAMPLE 1: IDENTIFICATION OF nGPCR-X

A. Database search

The Celera database was searched using known GPCR receptors as query sequences to find patterns suggestive of novel G protein-coupled receptors. Positive hits were further analyzed with the GCG program BLAST to determine which ones were the most likely candidates to encode G protein-coupled receptors, using the standard (default) alignment produced by BLAST as a guide.

Briefly, the BLAST algorithm, which stands for Basic Local Alignment Search Tool is suitable for determining sequence similarity (Altschul *et al.*, J. Mol. Biol., 1990, 215, 403-410, which is incorporated herein by reference in its entirety). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as

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the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension for the word hits in each direction are halted when: 1) the cumulative alignment score falls off by the quantity X from its maximum achieved value; 2) the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or 3) the end of either sequence is reached. The Blast algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The Blast program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 10915-10919, which is incorporated herein by reference in its entirety) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm (Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 1993, 90, 5873-5787, which is incorporated herein by reference in its entirety) and Gapped BLAST perform a statistical analysis of the similarity between two sequences. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a GPCR gene or cDNA if the smallest sum probability in comparison of the test nucleic acid to a GPCR nucleic acid is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Homology searches are performed with the program BLAST version 2.08. A collection of 340 query amino acid sequences derived from GPCRs was used to search the genomic DNA sequence using TBLASTN and alignments with an E-value lower than 0.01 were collected from each BLAST search. The amino acid sequences have been edited to remove regions in the sequence that produce non-significant alignments with proteins that are not related to GPCRs.

Multiple query sequences may have a significant alignment to the same genomic region, although each alignment may not cover exactly the same DNA region. A procedure is used to determine the region of maximum common overlap between the alignments from several query sequences. This region is called the consensus DNA

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region. The procedure for determining this consensus involves the automatic parsing of the BLAST output files using the program MSPcrunch to produce a tabular report. From this tabular report the start and end of each alignment in the genomic DNA is extracted. This information is used by a PERL script to derive the maximum common overlap. These regions are reported in the form of a unique sequence identifier, a start and the end position in the sequence. The sequences defined by these regions were extracted from the original genomic sequence file using the program fetchdb.

The consensus regions are assembled into a non-redundant set by using the program phrap. After assembly with phrap a set of contigs and singletons were defined as candidate DNA regions coding for nGPCRs. These sequences were then submitted for further sequence analysis.

Further sequence analysis involves the removal of sequences previously isolated and removal of sequences that are related to olfactory GPCR's.

nGPRCR-x cDNAs were sequenced directly using an ABI377 fluorescence-based sequencer (Perkin-Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM™ Ready Dye-Deoxy Terminator kit with Taq FS™ polymerase. Each ABI cycle sequencing reaction contained about 0.5 µg of plasmid DNA. Cycle-sequencing was performed using an initial denaturation at 98°C for 1 minute, followed by 50 cycles using the following parameters: 98°C for 30 seconds, annealing at 50°C for 30 seconds, and extension at 60°C for 4 minutes. Temperature cycles and times were controlled by a Perkin-Elmer 9600 thermocycler. Extension products were purified using Centriflex™ gel filtration cartridges (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product was loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B tabletop centrifuge) at 1500 x g for 4 minutes at room temperature. Column-purified samples were dried under vacuum for about 40 minutes and then dissolved in 5µl of a DNA loading solution (83% deionized formamide, 8.3mM EDTA, and 1.6 mg/ml Blue Dextran). The samples were then heated to 90°C for three minutes and loaded into the gel sample wells for sequence analysis using the ABI377 sequencer. Sequence analysis was performed by

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importing ABI377 files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp were obtained. Potential sequencing errors were minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers annealing at different locations until all sequencing ambiguities were removed.

The following Table 5 contains the sequences of the polynucleotides and polypeptides of the invention. The transmembrane domains within the polypeptide sequence are identified by underlining.

TABLE 5

The following DNA sequence Seq-2157 <SEQ ID NO. 1> was identified in *H. sapiens*:

```
TTAATCTTTGGGATCCTTTCCCTGACTCTGCAGCTGGGGGCCACCCCTCCCCAACCTGGT
AGCCAGCTGGGGGTCTAGTCTTTGGTAGGTTAAAGCAGAAGGTCTCTGGACTAGGACATC
CTACGCATAGTGAGGGCTGAGGTACCATAATGACAAATGGAGATTATGTGAAAGTTTATA
TACTGAATGTTGAGGAATTCAGCCTTGCCCTCATCTCCCCTTAACAAGATGCAGACACCT
GGATGCAAAACCCCCAGCAGGATGGTCTGGGAGAAAATCAGGAATGATTACACAGAAAAC
TATGCAAAAACAAGGCAATTATCAATTCCAGGCAAAACAAAATGCTGTGCATGAAAGGAG
GTTATCACATGATGCTTACATTGTTAAAATAACTTAAGACCTAACCAAAATTATGGTACC
TATACAGGGAAGATGATGGGGCAGGGAAGGGGATTTTAAAAAACTAATTCTTTGTTCTCT
GAAGTAGAAAATCAGAAGATAATGTTTAAAA
```

The following amino acid sequence <SEQ ID NO. 121> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 1:

```
LNIIF*FSTSE NKELVF*NPL PCPIIFPV*V P*FWLGLKLF *QCKHHVITS
FHAQHFVLPG IDNCLVFA*F SV*SFLIFSQ TILLGVLHPG VCILLRGDEG
KAEFLNIQYI NFHIISICHY GTSALTMRRM S*SRDLLL*P TKD*TPSWLP
GWGGVAPSCR VRERIPKI
```

The following DNA sequence Seq-2158 <SEQ ID NO. 2> was identified in *H. sapiens*:

```
GCCTGGTTGGTCATGCAGGCCTTTGCAGGCAATGTGAGCTGTCAGTCTAGGGGAAAGTGC
AGAAGTGCCTTAAACTGGGGGCCTGATATGATCAGATTTCAGCTGTGAAAAAAATCACAA
CTGGATTCAAAAACAGGGTGCAGAGTAGAGAGGGTGTCATGTGGATGTGGACAAATTCAG
GACTATTACAATTTTCCAGGCAAGAGAAAATGGCACCTGGACCTGGAGGGTGATTGTGAC
AGCAGTGGAAAAAGTGGATGAATTCCAAACACTTGGAGAAGAAACATCCCATCCACATGT
CTTGCTGGTGGATTAGCTGGGCCTGGGGGCAGAGGGAGAGACTAGTGTCAGGGATGACTC
CATGGTTCTAACCCGATTGGGTCTTGAAAGTACCTGGGCACAAAAAAATGATGAGTGTGT
GAGGTAATTGATATGTTACTTACCTTAAGTTAGCCATTCCACAATGTACCCATATATTAA
AATATGATGTTTATATATTTTTTTATTCATTAAAGAAATAATTTTTAAGTACCTAGGACA
GTTTTTAAAAATATTGATGCCAGATTCCCATCTCTAGAGATTCTGATTTAATTGGTCTGC
```


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TGCTGGGGTTGGAGGAGAGGGTAAGTGGTTGCGGCAGC

The following amino acid sequence <SEQ ID NO. 122> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 2:

LPQPLTLSSNPS SRPIKSESLE MGIWHQYF*K LS*VLKNYFF NE*KNI*TSY
FNIWVHCGMA NLR*VTYQLP HTLIIFLCPG TFKTQSG*NH GVIPDTSLSL
CPQAQLIHQQ DMWMGCFFSK CLEFIHFFHC CHNHPPGPGA IFSCLENCNS
PEFVHIHMTP SLLCTLFLNP VVIFFTAEI* SYQAPSLRHF CTFP*TDSSH
CLQRPA*PTR

The following DNA sequence Seq-2159 <SEQ ID NO. 3> was identified in *H. sapiens*:

CCTCTGTCCTCGACATGTCCTGTAAGCTGGAAGCCGGGATCAGATTCAGATCCATTTTTA
TTTTAAGTGTTATGCAAAAAGACACCCAGTGAAGGTGTTAGAATGAGCCATGGCAGTGGA
TGGGGTTCGCAGGACCCCTGCGGAAGGGGGACGTTTAAGGGGCAAGCGGAAAAGGAGACA
CCTGGAATGGGGGAGGAGGAGCAGCGGGGCGAGGCGGGGGCGGTGCCGCGTGGTCTGCGA
GCCCGGATATTCCCTGGGGAGCGCACCTGCGACTTCACCTCCAGTCCCTCCCCGGCTGGG
GCAGCGGGGCGCGGGCGCTCGGGAGAGGTGGCGCTGCCTACTCGGCCTCATCTTGCTGAG
AATGCGACGGGGCGACAGCTTCCTGTCTTTTCCAGTGGCTTTTGGCATCCCCAGAGGAAA
AAACGGGGAGACCCGCTTTGGCCTCAGGAAGCGCAGAAACACTGTCCTGGCTCCGCGCGC
AAGGGCGAGAACCTAGGGGACCCGCCTAAAGCGCCGTTGGGGCTGAGCACCGAACTCGCA
CAGCTCCGGGCAGCGACCCGCGATGCGGCATCCTTCCGTCCGGTCGGAGCCCTCCTAGCC
CTCAGCGCGTCTATTCCTAGCTTCGGTCCCCGCAGCCATATAAGCAATGACACCCTCGCC
GACTCGCCTGCCAGCTTGGCCGCCTCCCTGCAGAGGGCTGACGCTTC

The following amino acid sequence <SEQ ID NO. 123> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 3:

SVSPL QGGGQAGRRV GEGVIAYMAA
GTEARNRRAE G*EGSDRTEG CRIAGRCPEL CEFGAQPQRR FRRVP*VLAL
ARGARTVFLR FLRPKRVSPF FPLGMPKATG KDRKLSPRRI LSKMRPSRQR
HLSRAPAPRC PSRGGTGGEV AGALPREYPG SQTTRHRPRL APLLLLPHSR
CLLFRLPLKR PPSAGVLRTP STAMAHSNTF TGCLFA*HLK *KWI*I*SRL
PAYRTCRGQR

The following DNA sequence Seq-2160 <SEQ ID NO. 4> was identified in *H. sapiens*:

TTTCTCTCTTTAATTCTTCCTTTTATCATTAAAAAGGCATGAATTATCGTGCTGTATAAA
TAGAAAAATATGATAATGTGTGTGCATCTTGAAGAAGAAGGCTCTCATTCCATTTAAAAA
ATAAATTCCAGATTAGGAGGAGCCAGATTGTAACATTTTGGATCTACGACCGCTATTTGC
TTTGCCACCTGAATGACACAAAGAACACTGTTTGTGCAGTGTTGTGTGTGCCTCTTTATA
GAACTTGCATGTTTTCCAATTTGTATACATGCATACTTTGTTTTATTGTACTTTATTGCA
CTTCTCAGATTTTACAAAGATTTGAAGGTTTGTAGCAACCCTGCATAGATCAAATCTGTT
GGCCTAATTTTTCCAACAGCATTTTCTCATTTTATGTCACATATTGATAATTATTGCAAT
ATTTCAAGGTTTTCATCATTATTTTATCTGGTATGG

The following amino acid sequence <SEQ ID NO. 124> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 4:

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SLFNSSF YH*KGMNYRA V*IEKYDNVC AS*RRRLSFH LKNKFQIRRS
QIVTFWIYDR YLLCHLNDTK NTVCAVLCVP LYRTCMFSNL YTCILCFIVL
YCTSQILQRF EGL*QPCIDQ ICWPNFSNSI FSFYVTY**L LQYFKVFIII
LSGM

The following DNA sequence Seq-2221 <SEQ ID NO. 5> was identified in *H. sapiens*:

ATAGGCCAACAAGGTGTGAAATGTCACCTCTTGTATTTTACGTCGAGGCCAGCGTGAACA
GATTTTAAGTCTGGTTTCTGTAGGGCTCCATGGCAAGGGGGCTGGTGGGGCACCAAAGAC
AGACATTTCCTGCAAGGCTGAGGGCGCCGGCCTGCCTTTCCCAGTGCTTCCAGTTCACTG
CCGTTTGGCTGCCAGGAAGGCTAATGTCTGACACGCCCTCTTTTGGCATCAAATAACCAA
AACTAGTCAGTTCTAGTAAATTTAGAAATTTACCAAGAGCTGGAGTCCCCTTTTCATTAA
ATCCATATGCTTACTGGAAGCTAACGGGGGTCATAATACAATATATTGAATGAGACAAAC
ACTATGAAAAGAATTACACTAATTTTTGTTGTAGTAAAATCACAAACTTTCATTTGCATG
ATGAAAAAATACATATTGAGGCAGAACTCTACGATTGGCATGTTAGGTATGAAATTAAAG
GCCTGGGAGCATGAAATCGTCCTTTAGTATCTGGGGCTGATAAGATTTTTAATCACTTTT
ATATGAGACCACAGATTATTTATAATCGACTCACTTAAATAGTCTAACTGATATGGTTGA
GGTAACTTTAAAACATTTTTTGCTGAATGACTCACCC

The following amino acid sequence <SEQ ID NO. 125> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 5:

V SHSAKNVLKL PQPYQLDYLS ESIINNLWSH IKVIKNLISP
RY*RTISCSQ AFNFIPNMPI VEFCLNMYFF IMQMKVCDFT TTKISVILFI
VFVSFNILYY DPR*LPVSIW I**KGDSSSW *ISKFTRTD* FWLFDAKRGR
VRH*PSWQPN GSELEALGKA GRRPQPCRKC LSLVPHQPPC HGALQKPDLK
SVHAGLDVKY NTSHFTPCWP

The following DNA sequence Seq-2222 <SEQ ID NO. 6> was identified in *H. sapiens*:

TTTTATTCTCCTCTGTACCCTTCTGCTTATCAGAATATCTTCCATAGATACTGGTTTGTA
ATAGATTATAAATAATTTACATGTGGCTGAAAATGTCCCCATAGCTAGACAAAGTGAAAT
TCTGTTTCCTGACCAACATTCCCCCATCTTACTCTCTAAAGGTAACCACTGCTACACTGA
TTTATTTATTTTTAAGATACCAAACTGCAATCACAGAATAACACTGATGTGCTAGTTGTG
TTCTTCACATAACAAGGTGCACACTTTAAAAAATCATTTTCATTAAGCTATTATTTAGGT
AAAGTAAAATTCACTCTCTTTAATGTACAGTTCTTCAAGTCTTGAAAAGTGCATACAGTT
GTGTAAGTATTACCAAAATCAAGCCATACAACAGTTGCATCACTCCAAAAAGGGGCATCC
TGTGCCCCTTTGCAATCAGCCTGTTCTCCACACCCCAACCCTGGCAATGAACTATTTGTT
TTCTGACCCTCCAATTTTGATAGCTGTAGGTTTTCATTTTGCATTTTCATTTTAATTCTG
TTCTATGTATTTTTTATTTCCCTTGAGGCTTCCTCATTGACTCATAAATTAACTAGATAT
GTGTTTAATTTCCAAGTTCTTGGAGACTTTTTCTGTT

The following amino acid sequence <SEQ ID NO. 126> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 6:

LFSSVP FCLSEYLP*I LVCNRL*IIY
MWLKMSP*LD KVKFCFLTNI PPSYSLKVTT ATLIYLFLRY QTAITE*H*C

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ASCVLHITRC TL*KIIFIKL LFR*SKIHSL *CTVLQVLKS AYSCVSITKI
KPYNSCITPK RGILCPFAIS LFSTPQPWQ* TICFLTLQF* *L*VFILHFH
FNSVLCIFYF P*GFLIDS*I N*ICV*FPSS WRLFL

The following DNA sequence Seq-2223 <SEQ ID NO. 7> was identified in *H. sapiens*:

CAAATTTTTAATTTATCAGGCCCACGATGGGACGAATCACCTTCAGATTCCTTTATTTCT
CACAAACGAACATGGCAGCCAGCGAGGATCTGTCGTGAATGTGTGGGTGAGGCACACACG
CCACCACTGCCTTCGAAAGGCGCAATGACAAGGTTCACCCAACAAATACACAATAGGTTG
GGGGAGACAATATATGTATTTTCGGTTGGCATTTCAAATTATGCTGTGTTTATTCTAATG
TTAAAATCAATTTGTATTCTTCCACATATACAGCCACCTCTTAATAGTACATTTGAGAAT
TCTTTTTCCTGCTTCCCGGTCAGGACTGGGATTCAAAATCTGCCGTGGTTGATTAGCTTG
CTGATTTTTAAAAATGAATTTTCCCTTTAAAAATAAATCCCTCTTTTGGGGGCAACTAAC
GTTCTAACTTAGACCTTGGGAAGCTGTGGAATTTTATTCCTGTGTTCAACATCCAACCAA
ACTGCTTCCCTTCAAGTACGACTGGAATTTGTAATATAATCATCAAATTTCTATCATGAA
ACATTTGCATCCATATTGAAGTGTCTACATTCAAGGGAA

The following amino acid sequence <SEQ ID NO. 127> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 7:

FP* M*TLQYGCKC FMIEI**LYY
KFQSYLKGSS LVGC*TQE*N STASQGLS*N VSCPQKRDLF LKGKFIFKNQ
QANQPRQILN PSPDREAGKR ILKCTIKRWL YMWKNTN*F* H*NKHSII*N
ANRKYIYCLP QPIVYLLGEP CHCAFRRQWW RVCLTHTFTT DPRWLPCSFV
RNKGI*R*FV PSWA**IKNL

The following DNA sequence Seq-2224 <SEQ ID NO. 8> was identified in *H. sapiens*:

CCTCCTTGGTGTCAGGGGAAACCAGCTCCCCATTCAAACCTTACTTGAATCATCCAGGCC
CTGTTCCAATTGTTGGCCTGGCTCAAGTCTGGCCCATCTGCTGCTGAGCCCAGAGAGGGG
TGCCGGGGTTAGCTGGGGACTGGGTTCGCCTGGCCTGGAGGGTATGAGAGGCTTCAGCCA
GCCAGAGCCACTCTGTGCTGACAGTCCAGCATCTCAGTACTCAAAGCCCCCACATGCTTG
TGAGATAGGGTTGGGGGGGTCAATGATTAAGGAATGCAGAGCCCTTGACAATCATACACG
CATGCGCAGCTGGCCCATGCCCCTTGTCTGAAACCTTGGCTGCCTGCTCACCACCTTGAG
CAAGAAGGCCAAGTTCCTTATGGCCTACAATGACCTCTCTGGCCCTGGGCCCCTCCCAGC
GTCATCCCACTCCACTCCCTATTCCCACTTGTAGTTGTTGCTTGTCTCTGTGTTTTCATT
AATGTCTTCTCTCTCTGCAGGGCTGCCTCCTGCTTATTCTTCCAGATATGGCTCTTACTT
TCCTGACTACCTC

The following amino acid sequence <SEQ ID NO. 128> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 8:

PPWCQGKPAP HSNLT*IIQA LFQLLAWLKS GPSAAEPREG CRG*LGTGFA
WPGGYERLQP ARATLC*QSS ISVLKAPTCL *DRVGGVND* GMQSP*QSYT
HAQLAHAPCL KPWLPAHHLE QEGQVPYGLQ *PLWPWAPPS VIPLHSLFPL
VVVACLCVFI NVFSLCRAAS CLFFQIWLLL S*LP

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The following DNA sequence Seq-2225 <SEQ ID NO. 9> was identified in *H. sapiens*:

GCGCATATTACTATTTTAATGGTCAAAGTAACTCTGTGAGATGTGATTACACTGTTTTCC
AGATAAATGACTTGTGGCTCAGTGTGGCCAAGTAACTTGTGTAAGGTTACACAGCAATCG
ATTGGCAGATCAGGACTTGCATTCCAGTCTGACAAACTCCAAAGCTGTTGCTGAAGCAGC
CTTTAAGGCACTGTACCTGATGATTGAAGATGACTGTTGCAAAAAACCGAATAGGGCATT
TTGATAAAAGAAATGCTCTTTTGTGGCCAAAATATTTATGCTTCTTCCTCAGAGTTATGC
CTTATTTTTCTGCTGTTGTATATTTTTACTTCCTACTTTGCCCAGAGAAGGAAAAATATA
ACCCACACTAAAGAACTGGATCCATTTAAGTCATTAATTTCTCAAAGAGAAATCATG

The following amino acid sequence <SEQ ID NO. 129> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 9:

*FLFEKLM
T*MDPVL*CG LYFSFSGQSR K*KYTTAEK* GITLRKKHKY FGHKRAFLLS
KCPIRFFATV IFNHQVQCLK GCFSNSFGVC QTGMQVLICQ SIAV*PYTSY
LATLSHKSFI WKTV*SHLTE LL*PLK**YA

The following DNA sequence Seq-2226 <SEQ ID NO. 10> was identified in *H. sapiens*:

TTTCTGCAAGCTAGGAAGTGGACTCTCACCAAATAGTGAATTTTCCTGACTTTGATCTTG
GCCTCCCAACCTCCAGAACTGTGACAAATAAATATCTGTTGTTCTAGCTACCCAGTTATG
GTTTTTTGTTATAGCAGCTCAATTTGACAAATACGTGGACACAAGCATTCATCTAGCAGT
CACACAGATATAGAATTACAGACCACAGGAATAATAAAAAATGTACACTGTGCTTTTAAT
AGAGTATATTGGGGGCCCCTTGGGCAGTACATGAGACTGCTTCTCTGACGATATGACAAA
CTGAGCCCTGAGGGACTGGTAACAGTTAACCAAGTAAAGGATGAGGTAGCCTTTCAGGAT
GGGGAAAGTGAATGCACTGAGGTCTTAAACCAAGAGGGAGAAACCCATCAGCTGACTGAA
AGAAAAGCTAAGCCAAGGAATTTGAATATGTAGTCTAGAGAAGAGTGGGGTATGGTGGTG
GGATGGGAATGG

The following amino acid sequence <SEQ ID NO. 130> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 10:

FLQARKWTLT K**IFLTLIL ASQPPEL*QI NICCSSYPVM VFCYSSSI*Q
AQI
NICCSSYPVM VFCYSSS
IRGHKHSSSS HTDIELQTTG IIKNVHCAFN RVYWGPLGQY MRLLL*RYDK
LSPEGLVTVN QVKDEVAFQD GESECTEVLN QEGETHQLTE RKAKPRNLNM
*SREEWGMVV GWEW

The following DNA sequence Seq-2230 <SEQ ID NO. 11> was identified in *H. sapiens*:

GAAAGGGATTCTGGTTATTCTTGGATTTTTTTTAATGACAATAAATTTGCAATCTTCAGA
CAATATGAAACATAATACTAAACAATATAGAAAGCTCCCTTTTAGGTTTAGTAACATTTC
CACATTTGGTAGAGTCATCTCCCAGCTTCTGTGTTTCTGAAGTCTGATCACAATAAGAAA
TTAAGCCTGTGACTGTTCTGTGAAGAATGAAAAGAACAATACACCCATCAACATGAAGGA
ATGTCTACACCCCAAAACTAACCCCAGTCACAACATAATTTCCCTTGCCAAAGCCCTGCA
GAGCTTGGAAAGCCACATTCAAAAACACCAGCTTCATTATCCCATTAGCAGTAAGATGAG
ACCTTATCAAGCATTTCATGTTTCATATCCTAAAAATAACCTAAGAATGTGAAAAAGTCA

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ATAAAAATATTTTTAAGTACACAAAATGAGCCAAAAAAATTGAGAATGCTTAATGCAAAA
TGAAAGTCTTTATGGAAGGGTCCTGCTTGGAGAGAAGAGGACAAACTAAAACACCTTAAA
TATCAAAGGCTACTTGTGTACAGCTAAGCAGCTGGTCTCTCTTCTTTCTAAACTGGGAAC
CGGAGATGTTTATGAGGAAAATATGAAGAAAAGGAGTAAAATTTTTCTCCTGGTACTTGT
GCATGT

The following amino acid sequence <SEQ ID NO. 131> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 11:

TCTSTR RKILLLFFIF SS*TSPVPSL ERRETSCLAV
HK*PLIFKVF *FVLFSPSRT LP*RLSFCIK HSQFFWLILC T*KYFY*LFH
ILRLFLGYET *NA**GLILL LMG**SWCF* MWLSKLCRAL AREIML*LGL
VLGCRHSFML MGVLFFSFFT EQSQA*FLIV IRLQKHRSWE MTLPNVEMLL
NLKGSFLYCL VLCFILSEDC KFIVIKKNPR ITRIPF

The following DNA sequence Seq-2231 SEQ ID NO. 12> was identified in *H. sapiens*:

TAAGAAACATAGAATTTTAAATGATAAATGCTATAGAAATAAGGAAAATATTTTAAAATA
ACTTTAATCAGGTTTAAAAGTATGGAGTAAAACATTAAAACCAGTTAAAGTAAGAAGAAA
AGGAAACATAAAATAGGTCATAACATAAAATAAAAATTAAAGTTGAAAGGCAAGAAGTTA
CAAAGGGAATTAAAACAGAATAAATTAGAAACAAGATTTTCTAAAACTACATAGATGTGC
AAAGGTGTGTTTTCAATAATGAAGAGTAAAATTATAGCTGAAAACATTCTGTGGATACGA
GTCTTAAACAAGGTCTTCCTTAGCATGGAATTCCTCTTAATAAAGAGCCCACATTAACTC
GCCAGCCATTCATCCATCTAGCTCGTGTGCCTTCTTCATCTTCATATCCTTGGAGTCTGG
CACACTGTAGACATAGGTGCTTAATAGTTATAGAAAAAAATGAATAAATGTTCTGTGAAT
GCCTTTTATTTACAAGACACCTTTTGGGAGATGTTTGCATAA

The following amino acid sequence <SEQ ID NO. 132> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 12:

YANISQ
KVSCK*KAFT EHLFIFFYNY *APMSTVCQT PRI*R*RRHT S*MDEWLAS
CGLFIKRNSM LRKTLFKTRI HRMFSAIILL FIIENTPLHI YVVLENLVSN
LFCFNSLCNF LPFNFNFYFM L*PILCFLFF LL*LVLMFYS ILLNLIKVIL
KYFPYFYSIY HLKFYVS

The following DNA sequence Seq-2232 <SEQ ID NO. 13> was identified in *H. sapiens*:

AAGTTCACAAGTTTCTTATAAGAGTGTAACATAACATGTATCTCAAAGTTCCTGAGACAT
GTAACTCAATATGGTTCTTGTAGAGCAGCAGAAAGAGGAATGTGAAGAAGCTTCCAGATA
CATAATTCATGAGTGTCCGTAGACTCTAGGCTGAGTAGCTCCATCTGCCATTGTTTCCAA
AGGGTAACACCCTTCCCTGATTGTGCTACAAGAAGTACCAGTGTGCTTTTGGTGTTCATG
TCTAATATTCTCACTGCATCATAGCATTTATTTTTACAGGGAAGAAGAATCTATTACTCT
GATTTACAGAAAACTGAAATGCCTGACTGTCCAAAATATATTTCCGCCCTGCAACCCCCT
AAGCTTGATAGGAGCCAGAAGAAAGAAAAGGAAGCTGGGGCCAGGGAAGTTGCAAGGTCC
CTGGGAGGGCAGGAAGGGACTTTCCCTAATGCTGCATACTAACTAACCATACACCGTTTT
GACCGCTTTAATACTTAGTCTGCCAACTAAATC

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The following amino acid sequence <SEQ ID NO. 133> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 13:

SSQVSYKSV T*HVSQSS*D M*LNMVLVEQ
QKEECEEASR YIIHECP*TL G*VAPSAIVS KG*HPSLIVL QEVPVCFWCS
CLIFSLHHSI YFYREEESIT LIYRKLKCLT VQNIFPPCNP LSLIGARRKK
RKLGPGKLQG PWEGRKGLSL MLHTN*PYTV LTALILSLPT K

The following DNA sequence Seq-2233 <SEQ ID NO. 14> was identified in *H. sapiens*:

CTGGAAAGGGCGAAAGTGGGAGGACTGTGTAGAACTTGGTTGTGGGCCAGCACCGGCTGC
CGCTTGGTCCCCATGCCTGTGTTTTGTCATGAACTGCATTTCTGCAGGCCCAGCATTCTC
TGTGGCTATTTTTTGCTGCAGAGATTCAGGCCACGGAGGAGGCTTTTTGTCTGTACACCC
TCAGCAATGAATGGCCACAGCAGCTGCCTGTTACAAATGCCTTCCTCTTTCTGAGCTGCT
GGCGTGTGAAGGGTTTTATAGGCGGCCTTGCTTCAGATGGAAATAGAACAGCTCTGAACT
TGCTACCTATTACCTAGAAGTCATTTTCTGTAGTTATTCCCTTTGTGGCACCATCAAGCA
TGCACACCAGTAGCTGTCGAGGGTTTGGATATTTAACCAGCTCGTGTTCACACGCATGTG
GGTTTCGCCTGTGCCTCTGTGAGACCTCTGGCTAGTACCCATGTGTGTTGGATCTCATGT
GGCCTGTTCTCATTATTGGTATTGGCATTACACTTGAGACTGTGTGAGGGGCCGGGGTCC
CAGTGCAGTCACCTCAGGACCCAGAGCTGACCTGAACAGAACTTCAGTTTTTC

The following amino acid sequence <SEQ ID NO. 134> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 14:

LERAKVGGLC RTWLWASTGC RLVPMPVFCH ELHFCRPSIL CGYFLLQRFR
PRRRLFVCTP SAMNGHSSCL LQMPSSF*AA GV*RVL*AAL LQMEIEQL*T
CYLLPRSHFL *LFPLWHHQA CTPVAVEGLD I*PARVHTHV GFACASVRPL
ASTHVCWISC GLFSLLVLAL HLRLCEGPGS QCSHLRTQS* PEQNFSF

The following DNA sequence Seq-2234 <SEQ ID NO. 15> was identified in *H. sapiens*:

CCAAGTCCAAGAACTGACCTGTAACTAGACTAGACTAAACTTCCTGAGACACGGACCATG
TCTGCCATGTCCATTTTTGCATTCCCCATAAAGCACCATATCTAGCACACAGTACGTGCT
CATTAACCCTGTGAAATGAATATATGACCCAACCCTGAGGTAAGTTAGCCTGCAAGTATA
ACTTAATTAGGCACAATAATATCTGGGGAGAAGTCAGACCAATACCAACCACATAGATTA
ATTACAGAACAGTCTCAGTTGGGGCCATGTTGAGAATCTGCTTACTGGTGTCTGCGCAGG
AAAGGGTTAACGCAGCAGGTATGGGTTGCTCAAACCTTGCACATTCCAAAGAAAGGACTG
GGCCCTTGACTGGCTCCTGGGAGGTGACCTTTGAGCCCTTGGAAGATCCTGCCTGGTTGA
CTTTTTTTCTATGCCCCAGGCCTTAGGCCACACTATCAGTCTGACCAGTTTGTGCTAATA
AAGTGATTTATGGTGAATGTCTGGTTTTGTATGCCTAAGGCCCTGCCTGGGCTGTGCACC
AACAGTTTGACCTCTCAATAGCGTGGGGAACTAGAGACTGAGTGGCT

The following amino acid sequence <SEQ ID NO. 135> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 15:

KSKN*PVTRL
D*TS*DTDHV CHVHFCIPHK APYLAHSTCS LTL*NEYMTQ P*GKLACKYN
LIRHNNIWGE VRPIPTT*IN YRTVSVGAML RICLLVSAQE RVNAAGMGCS

NLAHSKERTG PLTGSWEVTF EPLEDPAWLT FFLCPRP*AT LSV*PVCANK
VIYGECLVLY A*GPAWAVHQ QFDLSIAWGT RD*VA

The following DNA sequence Seq-2235 <SEQ ID NO. 16> was identified in *H. sapiens*:

ATGATTTCTACACGATGATGTAATTTAGAAGTTGGGAATTCAGTGCCGTCATCCCAGTGA
CTTTTGGTCAACCAAATAGTGAACTTAACCAACCTCTTTCACATTGTTGTGATACAGAAT
CTGCCAGAGCTGAGGATATACATTATTATATTGAAAAATAATGTGGCATGTTTTACTTTT
TTGTTTCAGAACTTTTGGGAACTTATTTGCAAAGAAGTCCCCGCCATAAAGATCTATAAT
CTTTTCAACAACCTATTTGGGAAAATGCATGATAGGGCCGTGAAAAACATTATGTTCTAA
GACAAAGGCCTAATATTATCATGAGCAGCCTAGAGTGATGGAGAGAACACTAAATGCTGA
CTGGGTGCTGTTTTCAATGTGATCATCAAGTGGCCATGTGACCTTCAATGGATGCCAGCT
TTCCATGAGGCTTCAACTCCTCATTAACGAATGAGCAAAATAATACTTACCTCAACTTCT
TTCTAGGGCTATAGAGAAAAAAATGTTTAGAAAGAATGTAATATTTTAAGAGAGCATATT
GTTCTTTATTGCCATAATAAAAGTAATCATAATCTACATTATGAGGATCACCTTGGTATA
GTATTAAGCATGACACTGAGAAACAGGCGATGAGAGTTTCAGTTATGCCTTCTGAGTTT

The following amino acid sequence <SEQ ID NO. 136> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 16:

MISTR*CNLE VGNSVPSSQ* LLVNQIVNLT NLFHIVVIQN LPELRIYIII
LKNNVACFTF LFQNFWELIC KEVPAIKIYN LFNNLFGKMH DRAVKNIMF
DKGLILS*AA *SDGENTKC* LGAVFNVIIK WPCDLQWMPA FHEASTPH*R
MSKIILTSTS F*GYREKNV* KECNILREHI VLYCHNKSNH NLHYEDHLGI
VLSMTLRNRR *EFQLCLLS

The following DNA sequence Seq-2236 <SEQ ID NO. 17> was identified in *H. sapiens*:

GAACTGCTCCTTGCTTCCTTGCTCTATGCTCTATGACCTCATTTTTGTACCTTGTAATGT
CTATGTCCAGAGGGCCACTCAGGGGCATAGGATTCTTTTCGTGCTTTTCTGCTCTGTGCT
GTCAGGTCTTCTTAGCATCAGCCCTCATGTTGCCTGTGAATTGGCAATTGTTACACAGGA
CGGAGATCTTAGAGATTTGGTACAGACAGACTGTTGAAGTGTTGAGTATGAGAGAAAAAC
AGAAAATACCTTGAGTATGAGAGAAGAAACAGAAAATACCCTTTTGTCTTTCCCCCTTAT
TTCCTTTGGCTGGTTTTACAGATTTCCTTAATT

The following amino acid sequence <SEQ ID NO. 137> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 17:

TAPCFLALC SMTSFLYLVM SMSRGPLRGI
GFFSCFSALC CQVFLASALM LPVNWQLLHR TEILEIWYRQ TVEVLSMREK
QKIP*V*EKK QKIPFCLSPL FPLAGFTDFL N

The following DNA sequence Seq-2237 <SEQ ID NO. 18> was identified in *H. sapiens*:

CAGGCCCTGTCCCCTTACCCTGCAGGATGGAGGCAGAATCTGACCACCCCTGGTCCCAGC
CACCATCGGAGTCTACCTGCGCCCCTTCCCGCTCAGTGCAGCTGCCTTTGTGCTTTTGTA
CTCTGGGACCCTCTTGCTCAGAGCAAAAGCCAGTGTTCTTACAAGGCCTCCAGGACCCCA

BNSDOCID <WO_ 0166751A2 >

CAGATCTGTGAGCCGGAGCCCAATCTCAAGCAGCCCTGCTTTGGAGAGAGACATGTGTGC
AAGAGCCCTGGGGTCCCTGGTGGAGGAGGGCAGCCACCTCGGACCTCCGACCCAGCCCGG
CCTCCTGAGGATGGAAGTCTCAGAGGGAGACCAGCGGGCAGGTAGAGCGGTCGCAAGCTG
ACCTTGCTGAGTCCCCAGTTCCTGCACACAGAGTTGTGAGCAATACTAGGGTTTTGTGTG
AAGCCACTAAGCTTGGGAAGCCGGCAGCACCTGATGTATTGCACACTTAGCTGCTTAGTT
ATTTTTCAGTCCCCACCCTGTCCTCTAGAATTACAGCTCCTCAAGGGCAGGGACTTGACT
TCGCTCCCTGATGAGTCCCCAGCACCTAAACTGGTGTTTGACCAGTGACTGAGGCACTTG
GTAGATATTTAGCTTATTTGAGTATTAACTG

The following amino acid sequence <SEQ ID NO. 138> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 18:

VNTQIS*ISTK CLSHWSNTSL GAGDSSGSEV KSLPLRSCNS RGQGGD*KIT
KQLSVQYIRC CRLPKLSGFT QNPSIAHNSV CRNWGLSKVS LRPLYLPAGL
PLRLPSSGGR AGSEVRGGCP PPPGTPGLLH TCLSPKQGCL RLGSGSQICG
VLEAL*EHWL LL*ARGSQST KAQRQLH*AG RGAGRLRWWL GPGVVRFCLH
PAG*GDRA

The following DNA sequence Seq-2238 <SEQ ID NO. 19> was identified in *H. sapiens*:

TCATCTCACATAAAGTACAACCAAGCATTCTCAGAAAGTTCTTTGTGATGTGCGCATTCA
ACTCACAGATTTGAATATTCCTTTTGAGAGAGCAGTTTTTAGTCAGTGTTTTTGTAGTAC
CTGCAAGTGGATATTTGGAGCGATTTGAGGCCTAAGATGGAAAAGGAAATATCTTCACAT
AAAAACTAGACAGAAGCATTCTCAGAAACTGCTTTGTGATGTATACATTCAACTCACAGA
CTTGAAACTTTCTTTTGATAGACTAGTGTTGAAACACCCTTTTTGTAGAATCTGCAAGTG
TTCATGTGGAGCACTTTGTTGCCTATTGTGGAAAAAGTACATATCTTCACATAAAAACTA
GACAGAAGCATTCTCAGAAACTCCTTTGTGATGTGTGTGTTCAATTCACAGAGTTGAACC
TTTCTTTTGGTAGAGCTGTTTTGAAACACATCTTTTGTAGAATCTGCTTATGGATATAGG
AAGCTCTTTCAGGAATTGGTGGTAAAAGGGATATCTTCACATACAAACTAGACAGAAGCA
TTCTCAGAAACTGCTTTGTGATGTGTGCATTCAACTCACAGAGTTGAACATTTCCTTTCG
AGAGAGCAGTT

The following amino acid sequence <SEQ ID NO. 139> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 19:

N CSLERKCSTL *VECTHHKAV SENASV*FVC EDIPFTTNS
KSFLYP*ADS TKDVFQNSST KRKVQLCELN THITKEFLRM LLSSFYVKIC
TFSTIGNKVL HMNTCRFYKK GVSTLVYQKK VSSL*VECIH HKAVSENASV
FLCEDISFS ILGLKSLQIS TCRYYKNTD KLLSQKEYSN L*VECAHHKE
LSENAWLYFM *D

The following DNA sequence Seq-2239 <SEQ ID NO. 20> was identified in *H. sapiens*:

ACAGATGAGAAAATGTAGAACACTCCTTATAAAAGAAAATATAGGTAACCTAACTCATTT
TCAAGCGTTGACAATTCTTTTTGAATGCTTTACCACTGATGATCTGTGATCTCTGTGTGG
TACAAGATTTTCAAGGTCGCTCCTTGCTGTGGTCTGGATATATATACGGTCCCCACCAAA
CTCATGCTGAAATTTGATCTCATTGAGGTAGTGTTGGGGGTTGGGGCCTAATGGGAGGAG
TTCACGTCAT

BNSDOCID <WO 0166751A2 >

The following amino acid sequence <SEQ ID NO. 140> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 20:

R*EN VEHSL*KKI* VT*LIFKR*Q FFLNALPLMI
CDLCVVQDFQ GRSLLWSGYI YGPHQTHAEI *SH*GSVGGW GLMGGVHV

The following DNA sequence Seq-2240 <SEQ ID NO. 21> was identified in *H. sapiens*:

TGTGTTTTATATATATGAAGATTGGAGTGGTGAAAGCCATCCTCCCATTGTGTTTGGTCA
TTGCCATTTCAGTCCCCAGAACCACACTTAAAGGCTCTCTGGACCAGAGAAAATTCAGTT
AAGTATGAAGTGGCTACGCCAGCCCAGAACTTGATTTTATTGACCTGAAGTAAAAGCCTC
ACTTAGTACTTTTCTAAACAATTAAAGACGTGGTCCCCCACCTCCATTAAAAGATACAAG
GATCAATAAGAATATTGAAACACGTCGATGAAAAAAAAATTACAGGTACTATTTTTCAGT
GCTTTACTATATGCCTGGCCCAGTATTACATATTTTATAGATGTAGTTGCCCCAAAACCC
TGAATATTAACTGCTATATTTCCTATTTTTATTTTTCAAATGAGATAATTGAACCTTAAA
AAAAGCCAAGTAATTTTCCCAAACCCAAAAGACAGAAAAAGCCAGGGTTTAAACTCAGCT
TTCCAACTGCAAACCACTGCCTTATCTGGTATATCTGCCTTGGCCCAGATAGTGACCATC
ACAGGTCTCAGAGTCCATTCAAAGATAAATATGTATTTGGATTTAAAGGTCAATTCATTC
ACTTCATTGACAAGAAAATAGAAGCCCAGAAATAATAAGATACCCGGTGGAAAGAGCACC
AATTACACCACCAGCCATCTTGAGCCCCAGTCCTGAGTGTACA

The following amino acid sequence <SEQ ID NO. 141> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 21:

CF IYMKIGVVKA ILPLCLVIAI SVPRTTLKGS
LDQRKFS*V* SGYASPELDF IDLK*KPHLV LF*TIKDVVP HLH*KIQGSI
RILKHVDEKK ITGTIFQCFT ICLAQYYIFY RCSCPKTLNI NCYISYFYFS
NEIIEP*KKP SNFPKPKRQK KPGFKLSFPT ANHCLIWYIC LGPDSDHHRS
QSPFKDKYVF GFKGQFIHFI DKKIEAQK** DTRWKEHQLH HQPS*APVLS
V

The following DNA sequence Seq-2241 SEQ ID NO. 22> was identified in *H. sapiens*:

CCCTGACGCTGAGCCCTAAATCACCACCAACAGCACACTCATGGCCAGTCTCTTGGTTGA
ACTTTGCATGGTGCCACCTTTGATGCCCTTTAGTGACCCTCGTGCTCTTCAAATGAGAGA
AATATCATTGTCTGCTGTTGCCATAGTCCCTTCTTCCCCAGGCAGAGGCCGAAGACTGAG
GGGCTCACCAGCCAGCCTCAAAAGGCTTTGGTCCATGAAGCCCCCACACACTTCCTGTCC
GTTCCCATTCACTCCAGGCTCTGGGCCCCCAGATCACTTACAATGGCCTTTTCCCGCCGC
TTCCTGGCGTGCCGGATGCTTGGCGTTCTGTCTGAACACGGGCCTCTGCTCTCACATCTG
TCAGTGAACAAGCAAAGCAGAGGCACTCACTCTCGGGAGATACCATGGGGGTGGGGGCGG
ATCTGCTCCAGGACGC

The following amino acid sequence <SEQ ID NO. 142> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 22:

PDAEP
*ITTNSTLMA SLLVELCMVP PLMPFSDPRA LQMREISLSA VAIVPSSPGR
GRRLRGSPAS LKRLWSMKPP HTSCPFPFTP GSGPPDHLQW PFPAASWRAG

BNSDOCID <WO_ 0166751A2_I_>

CLAFCLNTGL CSHICQ*TSK AEALTLGRYH GGGGGSAPGR

The following DNA sequence Seq-2242 <SEQ ID NO. 23> was identified in *H. sapiens*:

AAAACAGACCAAAAAACTGAAGGACTTTTACAGCACTCATTTCCAGCCAGAGGAAACTAG
AAACGTTTGGTGGAAGAGGTGTCCTTTGAGCTGGCCCTTGAGGACTCTAATAGGGGATGA
ATAACTGTAGAAAGCTGGATTATTCCAGGAGGCAGAAGGCACGGGGGCAAAAACATAGAG
GTAGGAGAGCCTACGTTTTGCAAAGGAAGAATGATCAGTAATCTATTTTGGTGACAGCCT
AGAAAAAATATGGTGGAGTGGTGGGAAAAATGGGTTGGAATTAGGTTGGAACCAAATGGT
AACACACAGGTCTGGAATGTGACTTTAAGAAGTTTAGAATATTTGATAGGTACCATTGAC
CTACTGAAAAGCATTTGAGGAAGAAGGGCTTAATCAAAACCATGCTTTAGTGTGAACAAA
CAAACAATAATCAGGGATATGTGACAACAAATATTTGATAAAATCTAATGTCAGGAAATA
TTCTTGTTGTAACATAAGGAGAAAACTAGTAGGCTGTTGAAGTTTGATCCCCTGGAAGAA
ATAATAAGAAAAATAAAATAATAAATTATAATAATAGCCAACCTTTGTTAAACTCATATT
ATGCACCAGGCTCTGTCTCCAAGTTCCTTATAATAACAATCGAGTATTCACTCTGTGAGT
CCAGGTTTGCTGCAA

The following amino acid sequence <SEQ ID NO. 143> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 23:

AANLDSQS EYSIVIIRNL ETEPGA*YEF
NKGWLLL*FI ILFFLLFLPG DQTSTAY*FS PYVTTRIFPD IRFYQIFVVT
YP*LLFVCSH *SMVLIKPFF LKCFSVGQWY LSNILNFLKS HSRPVCYHLV
PT*FQPIFPT TPPYFF*AVT KIDY*SFFLC KT*ALLPLCF CPRAFCLLE
SSFLQLFIPY *SPQGPAQRT PLPPNVSSFL WLEMSAVKVL QFFGLF

The following DNA sequence Seq-2243 <SEQ ID NO. 24> was identified in *H. sapiens*:

TTTTTGTTACATGTGAGTGTGCACATGCACGTGTGCATGAGACTATGGGTTTAATTTCTT
CAGATAATTCTCTATGTACATGGAAGTGCAAAAGCCCAAGAGTGAAGAACACAAACTGTG
AAGTCATCGCTTAGAAGATATGACACATAATTATTAAGCTACAGTACTTAAGAGTGAGAT
AATGGCACAAGAATAGACACATAAAACCTATGGAAACGTAACAAGGAGTCCAGAAATACA
GTCCAGAATTTTGACATTGTAGGTCATAGGAAAAAGTCGAATGCTTCCATAAATCATGCT
GGAAAAACTAGTATCCATATTTATAAATAAAATGAAATTCAACTGCTACCTCACACAAAA
ATTCGAACACCCCCATTCCCAATCAATCCAGCTGGATTATAGATATTCATAATTTAAGTC
AAACAATTATAGAAGAAATACAGAAAGCTAAAGATATGATATCACATGTTATGGTATAAT
TTGTTAACCAACATACACAATGTAAACTGTAAAGGAAAAGACTCATAAATCAATGTCTTT
CAAAATTAAGAATGACTGGTAAACAAATGATCATGGACAGATCCCCGAAACAAGCAGCAC
AAGGATGGGAGATATTTGCAAGATGGAGGAATGATATACAGGATATACAGCAATGGAGGA
ATGATATATAGGATTACAGCAA

The following amino acid sequence <SEQ ID NO. 144> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 24:

LL*SYISFLH CCISCISFLH
LANISHPCAA CFGDLSMIIC LPVILNFERH *FMSLFLYSL HCVCWLTNYT
ITCDIISLAF CISSIIV*LK L*ISIIQLD* LGMGVFEFLC EVAVEFHFIY
KYGY*FFQHD LWKHSTFSYD LQCQNSGLYF WTPCYVSIGF MCLFLCHYLT

BNSDOCID <WO 0166751A2_I_>

LKYCSLIIMC HIF*AMTSQF VFFTLGLLHF HVHRELSEEI KPIVSCTRAC
AHSHVTK

The following DNA sequence Seq-2244 <SEQ ID NO. 25> was identified in *H. sapiens*:

AGACTATAGATAAATAAAAGGCAATACTTAGAGCAAAATATAATCCCCTAAATATTTTTC
TTGGATTTTGATATCTTGTCCATATTGAAGAGATGCCCTAGAAACATATAGCTTCTCTCC
TAACTTTACCATGTCCCAGGAGGAAATATTCCTAATGTTCTGTTCAAATTTTCCGTCCTT
TTTAAGTCAGCCATTTTTGTTATAACTCAAAATGTTATATTTAATATATACCAGCTGTAT
AAGAGTAACCTTGAATTTAGGATATGATAGACTAAAACGAAAAGCTTTTATCACAGCTTC
CTATATACATTTTCATCAACTCATATGGTACACATCTGGGCCTTTGATAGCTATGTGTGT
AAAAAAATCCCTGTTATCTTCAAAATTAATTTTAAATCTTGTGTTTTTCTCTTTTTCAGT
CACTTAAAAGGATAAATATTAATGGACATAATCATGAAACTATCTGTGAAAGTCATTTGA
AGATAGTGATAAAGGCGTATTGACAGAATCTACATTTGATACATTGAAAAAAATCATTGA
AAAAGAAGGCAGAAATAAATGAACAATGATTGAATACCAGTAAACTTGGTGCTTTGCACA
CTGCCTTTGATTTCATTCTCCCAAAATATCTGGGAAATAGATATTATTTGTCATTTGCAG
ATGAGAAAACTAAGGC

The following amino acid sequence <SEQ ID NO. 145> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 25:

RL*INKRQYL EQNIIP*IFF LDFDILSILK RCPRNI*LLS *LYHVPGGNI
PNVLFKFSVL FKSAIFVITQ NVIFNIYQLY KSNLEFRI** TKTKSFYHSF
LYTFSSTHMV HIWAFDSYVC KKIPVIFKIN FKSCVFLFFS HLKG*ILMDI
IMKLSVKVI* R***RRIDRI YI*YIEKNH* KRRQK*MNND *IPVNLVLCT
LPLISFSQNI WEIDIICHLQ MRKLR

The following DNA sequence Seq-2245 <SEQ ID NO. 26> was identified in *H. sapiens*:

TTGAATAGATTTCTAGTAGTGAAATTGCTGAGCTGTGTGGTAAACGCATGTTTAATTTTT
AAAGAAAATGCAAAACTTTCTAAAGTCATCAGATCAGACCATTTTACATTCTCACCAGCA
ATGTGTGAGGGTTCCAGGTTTTTTGTCTTTTATTATAGCCATTCTATTTCATGTGTACTG
TTATCTCATTATGGTTTTAATTTGTATTTTCTATTAGTTTTTCTGTTGCTGTGTAACAAA
TTACCACAAACATAGCAGCTTAAAACAACATTCTTTTTATTCACAGTTTCCATGGGTTAG
GAATCTGATTATAGGTTAACTAGGGTCTCTGTACAGGGTCTCACTGGGCTGAAATTAAAC
TTGCATGGGACTGCAGTCTCATTTGAGGAGTTCCTCCTCCAGGCTCACTGGTTGTTGACA
GAAATCAATTCCTTGATTTTGTAGGACAGAAGTCTCCATTTTCTTTTTGGCTATCAGCTA
GGGACTGCTCTTAGCTTCTACAGGCCACCCTAGAGGGGTCCTTGCCTTGTGGCTCCTTCC
AGAGGAAGTTCACCACCTGGTTGGTTGCAAAAGAATCCTTCTCACTTTTATTCT

The following amino acid sequence <SEQ ID NO. 146> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 26:

LNRFLVVKLL SCVVNACLIF KENAKLSKVI RSDHFTFSPA MCEGSRFFVF
YYSHSISCVL LSHYGFNLYF LLVFLLLCNK LPQT*QLKTT FFLFTVSMG
ESDYRLTRVS VQGLTGLKLN LHGTAVSFEE FLLQAHWLLT EINSLIL*DR
SLHFLFGYQL GTALSFYRPP *RGPCLVAPS RGSSPPGWLQ KNPSHFYS

BNSDOCID: <WO___0166751A2_I_>

The following DNA sequence Seq-2246 <SEQ ID NO. 27> was identified in *H. sapiens*:

TTAGTTATATTAGAAATACCTAAATCTAACTCACTAACAAACTTACATCATATAAATTGT
TTTGTTTCAGATGGATTATTTGGTATAAATTTTAAAATCAATCAATTAAGATGTCTTGAA
AGTTGTACTCTAGTCAAAATATTATACTAGGTAGATACTATGGAGGAAACAGAGAGGGCT
GTTTAAGACATGGCCGCCTGCATTTATTAAGATGGGAATGAATCACTGGGAAACTGCAGA
GACTGGAAAGGAGGACAGGTAAGACAAGATAGCCCTTCAGCAAATAAGAGGAGAAGGGTG
AGAATTGAGATGTTGGCTAGGATTAAGGTTAAAATGGATGGGTATATATGGTCACAACTG
GATTTTCAGGAATACTTGTAATCACAAACAGGCAATATCTTCCACTTCTCTTAAC

The following amino acid sequence <SEQ ID NO. 147> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 27:

LVILEIPKSN SLTNLHHINC FVSDGLFGIN FKINQLRCLE SCTLVKILY
VDTMEETERA V*DMAACIY* DGNESLGNCR DWKGGQVRQD SPSANKRRRV
RIEMLARIKV KMDGYIWSQL DFQEYL*SQT GNIFHFS*

The following DNA sequence Seq-2247 <SEQ ID NO. 28> was identified in *H. sapiens*:

AAATGTGGGCAGAGGCGGATGTGTACTGGTTTGGAGCAGAGGTTTTTACGCCCAGCACAT
GGTATGCCAGGTCTTTTCCCTTTGCCATGAGACTGGTAATGTTTCGGCTAATAAGGGCTC
CATCAGCATGGTTACCAGAGTGAAGCTGGGGAGTTGTTTGGAAAAATTCCTGAATTAGCA
GATCTGTACATCTCTGGGCTGAGGCTTGGGAACTTATAGTTTTAGAAAATTCCCCAGGGA
AAGTGTACAGACATCTGCAATTTACTTGGAAGTGGACAGGAAAAAGAGATGTACTGATGG
ATGAATAGAGGGACAGATAAATAACAAGACAAGATATACAGGTTGGAGCACTCCTTATCT
GAAATGCTTGGGATCAGAAGTGTTTTATATTTTAATTTTTTTTTATTTTGGGATACTTGC
ATTATACTTACTAGTTGAGCATCCCAAATCCTAAAATTCAAAATCCCAAATGCTCCAATG
AGCAGTTCCTTTGAGCGTTACGTTGGCATG

The following amino acid sequence <SEQ ID NO. 148> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 28:

CQR
NAQRNCSLEH LGF*ILGFGM LN**V*CKYP KIKKN*NIKH F*SQAFQIRS
APTCISCLVI YLSLYSSIST SLFPVHFQVN CRCLYTFPGE FSKTISSQAS
AQRCTDLLIQ EFFQTTPQLH SGNHADGALI SRNITSLMAK GKDLAYHVLG
VKTSAPNQYT SASAHI

The following DNA sequence Seq-2248 <SEQ ID NO. 29> was identified in *H. sapiens*:

TTATAGCTTCTAAAAAATTTTTATTTAAATGTTTATAAACAGAAAAATTAAAGACTAAAA
AAGACCTAACTCAAATTTTCTTTTTAAGTATTTTATGTTTTTAAAAGGAGTGACTGGTAT
AAAACACCAGAAGAGCTCTTAATGTTTAATGATGAGATTTAAGCAATTGGTGGAAATTGG
GAGCAGCAGCTCGATAGCTTCAAAGGCCTTCTCAAACCTCCACAGCTTAGGCTTCTATTA
ATATCTCTGCTTGGCTTTGGGAGACAGAAGGTGAAGAAACCATAAACATTTAGAGTTGAT
AGGGGTATAGAGAAGAAAACAGGATTAATAGGAGATACTATAACCCTGAGAATCCAGGTA

ENSDOCID <WO 0166751A2_I_>

TGGTGGGATCTCAGCTCCAAGTTGACACAGGAACACAGTTCTCCACAACCAAGCTATGGA
CAAATCTTAAGACTTCAGAGACCTGAGCAAGCGGAAGTTATCTTAGCAGTGACTGTGTCC
AACACTTTCCCATGGTACATGGTCTCCTTAGCAGTGGATCTGGTAAGTGAC

The following amino acid sequence <SEQ ID NO. 149> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 29:

SLTR STAKETMYHG KVLDTVTAKI TSACSGL*SL KICP*LGCGE
LCSCVNLELR SHHTWILRVI VSPINPVFFS IPLSTLNVYG FFTFCLPKPS
RDINRSLSCG GLRRPLKLSS CCSQFPPIA* ISSLNIKSSS GVLYQSLLLK
T*NT*KENLS *VFFSL*FFC L*TFK*KFFR SY

The following DNA sequence Seq-2249 <SEQ ID NO. 30> was identified in *H. sapiens*:

CGTAGTCATTTTTTTAGTTTGATGTAGCAAATGATTGAAAATAATCTAAATGCTGATCAA
CAAGGAACTGGTGCAATATAGTACATAACATTTACACAATGAAATTTTATGCAACCAGTA
AAGAATAAAATAGATCTATATGTTCTAATAAGGTAGATCTATATGTGCTAATTCTAAAAG
ATATATTAAGTGAGAAAGTCAATAGGCAGAACAGTGTACAGAGTATGCTCTCATTTGTTT
TAAAAATAAGGGTATAGATGCATATATATGTACATATATATACTTTCTATATATGCATAA
AACTAATTGGCTCATTTAACTGAAAAGTTGAGGGTTGAGTTGTCCTTCAGACTATGTCCA
GGGGCTCACAGGATGTTACTAGAAACTGCTCCTCACTCTGTAGCTTGACTGCACTTTTCT
CTGTGTTGGCTTCATTGTCAGCTTCTTCCATGCCATGGCAGCTCCAGACTTTCACAGTTA
CTGCAGTTCATGGCAGACACTATTGATCTCACTGTTCCTTTATTAAATATAACAGAGGAT
TTCCAGTCTTGTTTGAGTTATTTGCCCATCCTGTGGATCCCTCACTGTGAATGGAGGGAT

The following amino acid sequence <SEQ ID NO. 150> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 30:

RSHFFSLM*Q MIENNLNADQ QGTGAI*YIT FTQ*NFMQPV KNKIDLYVLI
R*IYMC*F*K IY*VRKSIGR TVYRVCSHLF *K*GYRCIYM YIYILSIYA
N*LAHLTEKL RVELSFRLCP GAHRMLLETA PHSVA*LHFS LCWLHCQLLP
CHGSSRLSQL LQFMADTIDL TVPLLNITED FQSCLSYLPI LWIPHCEWRD

The following DNA sequence Seq-2250 <SEQ ID NO. 31> was identified in *H. sapiens*:

CGAGGCAGGGCTCTGAGCGGGTCATTGTAAGGCCTAAATTAATTGGTGGCGGTGGGAAGG
AAGATGTGTGAGGGTCCACAGTGCTGGCAGGACCTGGCTTACAGGCACGAGCTATTAAGT
GGCATATGGGGGAGGGTCAGGGTTTTTTTAGGAGCCTGTTGGATACTCAAGTGGAATTGC
CTAGTGGACAGTTGTAACTGTGACTTAGAATCACCTTTGACTTTTTGTTCTGTCTTCCCC
ATCCATTCCACTGGCTGCTGAATTTGATCATCTTTTTTACCTTAGTGCAGTCTCTCTGAC
ATGGAACTTCTTTTCTGTTCCCTTCACCGTCCTGAACACACTCCTTGCCACATCAACCAT
GCATATCTGTGTGTATGAAGGAGCACTATTTTATGCTTCTTTCCGCTCTGCC

The following amino acid sequence <SEQ ID NO. 151> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 31:

RGRALSGSL* GLN*LVAVGR KMCEGPQCWQ DLAYRHELLS GIWGRVRVFL
GACWILKWNC LVDSCNCDLE SPLTFCSVFP IHSTGC*I*S SFLP*CSLSD

BNSDOCID <WO__0166751A2

MELLFCSLHR PEHTPCHINH AYLCV*RSTI LCFFPLC

The following DNA sequence Seq-2251 SEQ ID NO. 32> was identified in *H. sapiens*:

TATCAAGGTTACTCTGTGTGTTTATTTTACGCTCTAAGCCACCATTTGGTAACTTATAAA
ACCTCTGAGACGCAGTCTTATCACATGAAGGATAACATGTCACACTCACCCGGTGAAGCC
TAGATTGACATCAAACTCTGAGCAAAGTAGAACCTTTGGGATTCAGAGCCTCTGATTCAG
ATGCCAGTTACTCAGATGTTAGCTTTGAAGAGCTCTTTCCCCACCCACAGCCTGAGCAAA
GCTCCATCAAAACGAGGTTGGCTTCAACCCCTTCCAAACCAGATTAGGTTTCACGGTCAA
CACTGGCTGCTGGGAGCTGAGCAAGATGGTAGCGGCGCAGGTAGCAGAGGAGAATTCATG
GTGTCTATGCAGCCTGCCTTTCTCCCTGTGTGTTTTGCCTTCCCTTGTGTCATCTTAGTT
TTTTGGTTTGTCTTTCCTGTCCCACAATGTGTGAATTTCATGAACACGTATGCTTTGGCC
AACGATGTATTGTAAATACGCAGAGCAGTGGCTGGCATGAGGTCAGTGCTCTAATGTTTG
GGGAATTGTATTGAATCTGGTTTCATGCTATCTGATTCTTTCCACCAAAGCCTCCTACTG
GGTTATTGGGAGGAGCTTGTCATAGTGGGGTCA

The following amino acid sequence <SEQ ID NO. 152> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 32:

YQGYSVCLFY ALSHHLVTYK TSETQSYHMK DNMSHSPGEA *IDIKL*AK
NLWDSEPLIQ MPVTQMLALK SSFPTHSLSK APSKRGWLQP LPNQIRFHGQ
HWLLGAEQDG SGAGSRGEFM VSMQPAFLPV CFAFPCVILV FWFVFPVPQC
VNFMNTYALA NDVL*IRRAV AGMRSVL*CL GNCIESGFML SDSFHQSLLL
GYWEELVIVG S

The following DNA sequence Seq-2252 <SEQ ID NO. 33> was identified in *H. sapiens*:

GAGGGGAAGGTGGCTGGAGTACCCCTCCCCAACTCCTCCCCGGGGGTAGAAGGCCTTTTC
TGGCAATGTCTGCATCCCTCCAAGACCCCAGTTCCTCCCAGGTAGCTCTTGCTCCACGGC
TCCAGCCCCCATGGAGCTCTGTGAGTGCAATTATCCCCCCTTGTCCTCACAGCCATAGAG
GTGGTGACTGCTTCTCACTTTTGCTAGTGTCTGGGTGCCTCACCTGCCTTATTTGTTTCC
ATAACCCTTTCCACACCTCTAAAAGCTCTATGAGTAAAGTTTCCTCACTAGAACTATCTG
GGGTGAATCCCTTTTCCCCTCCAGGAATCTAAGTGTGCAGTCCATGAGGTTAGCCTCGCA
GGGCTCCCAGCAGGGCGGAGAAGTCCAGCTCAGAACTCTGGGGTGGGGAT

The following amino acid sequence <SEQ ID NO. 153> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 33:

IP TPEF*AGLLR PAGSPARLTS WTAHLDSWRG KGIHPR*F
GNFTHRAFRG VERVMETNKA GEAPRH*QK* EAVTTSMAVR TRGDNCTHRA
PWGLEPWSKS YLGGTGVLEG CRHCQKRPST PGEELGRGTP ATFP

The following DNA sequence Seq-2253 <SEQ ID NO. 34> was identified in *H. sapiens*:

GGCCCATGTGGGGCCTTCACTTCCGCCTCCTGGCCTGTCAGGTGGAAAGAACATGAAGGC

ENSDOCID <WO 0166751A2 I

CAAGCTCAGCGTGGCCCACGGCTTGGCTCAAGGGTTGCATCCTGGCCTGGCTAGGGTGGA
TCCAGATCGAGGCAGTATATATTCAGTTGAACCCTGTATCTGGCCCAGTTCAGTACATCC
CCCAAAATGTGGGGGACATGTTCCTGGGAGGTGCACACAGGTCTGCTTCTGTTCACCTGA
ATTATTGCAATCCAACAGATGGGGCCTTACCTG

The following amino acid sequence <SEQ ID NO. 154> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 34:

R*GPICWI AIIQVNRSRP VCTSQEHVPH ILGDVLNWAR
YRVQLNIYCL DLDPP*PGQD ATLEPSRGPR *AWPSCSFHL TGQEAEVKAP
HG

The following DNA sequence Seq-2254 <SEQ ID NO. 35> was identified in *H. sapiens*:

AAAACTGTTCTAAAAGTACAGTACATATATTCATAAAAAAATTAATGTCAATATCCTCAA
ATTATGTCACTATTCACTAGGAAAAGTATTTAGAAAATATGATAAAAATGTGACATTTAC
ATTAGTTTCTAATGCATAAAACACCTACCAGTAAATCTATCAAAAGCAATGCAATATCTT
TATGCAGAAAATCAGAGATTATTTATAAGAAAACATTTATGTGATATCATATACATGAAT
TGAATGACTTAATATAAGAAAAATGTTGAGTTTTTTCAAATTGATCTATCAGTTTAGTGA
AATTCTAGTAAAACAAAAAGTCAACAGAGGTGTGGTTTTTGTTTACATGTGAGTGTGCAC
ATGCACGTGTGCATGAGACTATGGGTTTAATTTCTTCAGATAATTCTCTATGTACATGGA
AGTGCAAAAGCCCAAGAGTGAAGAACACAAACTGTGAAGTCATCGCTTAGAAGATATGAC
ACATAATTATTAAGCTACAGTACTTAAGAGTGAGATAATGGCACAAGAATAGACACATAA
AACCTATGGAAACGTAACAAGGAGTCCAGAAATACAGTCCAGAATTTTGACATTGTAGGT
CATAGGAAAAAGTCGAATGCTTCCATAAATCATGCTGGAA

The following amino acid sequence <SEQ ID NO. 155> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 35:

FQ HDLWKHSTFS
YDLQCQNSGL YFWTPCYVSI GFMCLFLCHY LTLKYCSLII MCHIF*AMTS
QFVFFTLGLL HFHVHRELSE EIKPIVSCTR ACAHSHVNKN HTSVDFLFY
NFTKLIDQFE KTQHFSYIKS FNSCI*YHIN VFL*IISDFL HKDIALLLID
LLVGVLCIRN *CKCHIFIIF SKYFS**IVT *FEDIDINFF MNICTVLLEQ
F

The following DNA sequence Seq-2255 <SEQ ID NO. 36> was identified in *H. sapiens*:

ACCCCCATTTTGGGACTCACCTGCCCTGCATCAAGGGTACATGCACAAAAAATTTCGCAG
AGATAATTTTAATAGTGATAGCCCCAAACTGCAACATCCATCCTCAGTAGAATGAATTCA
GTTATTGTCCAGATATTGAAATGCTATATAGCAATGAGAAAGAGGGAACTATTGCTACAT
TCAGTTATTGTCCAGATATTGAAATGCTATATAGCAATGAGAAAGAGGGAACTATTGCTA
CATACCACCACATAGCTAGATCTCCAGACATGTTGAAAACAGCAAACCACCCCAAAAGAG
CATGCGATTCTGCTTATGTGTAACTCAGAAAGAGGCAAAACTAATCCATGGAGATTAATC
AGACTACCTGTTGCCTTTAAGGTGGATATTGACCGGGAAAAGACATGATGAAGGTTTTTG
GGATCTGGTCATATTCATAGTCTGATCTCTGTAGTAGTTACA

The following amino acid sequence <SEQ ID NO. 156> is the predicted

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amino acid sequence derived from the DNA sequence of SEQ ID NO. 36:

VTTTEI RL*I*PDPKN LHHVFSRSIS TLKATGSLIN
LHGLVLPLSE LHISRIACSF GVVCCFQHVW RSSYVVVCSN SSLFLIAI*H
FNIWTITECS NSSLFLIAI* HFNIWTITEF ILLRMDVAVW GYHY*NYLCE
IFCACTLDAG QVSPKMG

The following DNA sequence Seq-2256 <SEQ ID NO. 37> was identified in *H. sapiens*:

TTGGGCAAAGTGGCTGTATTATCCTTTCTATGGCTCTAATACCAGTAAATCAGGGTCTTG
ACTTCAGATTTCTTAAAAATTTTCTCTGCTAGTGCCAGAAATTGTTCAAGTCTAAAACAA
TAACACCAGCAACAACTTTATTTACCATATAGGTGATCTTTCCAGGCTGAACGCAGTTTA
CTTTCTAAAAATTATTACAGTATTGAATAACGCAAGAGTTTTAAGATCTTATTATTTAAA
AAAAAATGTTTTCTACAATTCCCAATTGAAAGAGCCAGCCAGGTAAAAATTCAATCAAGG
AAAACAAAGCCTTAAAAACACAGAGATGAATGATATTTGAATTAAATAATTGTATCCTAA
ATGCATAGCAT

The following amino acid sequence <SEQ ID NO. 157> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 37:

WAKWLYY PFYGSNTSKS GS*LQIS*KF
SLLVPEIVQV *NNNTSNNFI YHIGDLSRLN AVYFLKIITV LNNARVLRSY
YLKKNVFYNS QLKEPAR*KF NQGKQSLKNT EMNDI*IK*L YPKCIA

The following DNA sequence Seq-2257 <SEQ ID NO. 38> was identified in *H. sapiens*:

AGAAAAAAAGAGACAAGCCAAGGGAAAAAGGGGGAGAAACAGAGAAACAGTAGGCGGAGT
GGTGTGCTGAGTGGAGGACAGTGTTGAAGCCACCTAAGTCGTGCCAGGTGTCACTTAGTG
GCAGCCATCATGGGCCATCTACTCTGTCTGGATTATGTGAACAGACAGGCAAAGGGCTCA
GCCCTCCCCTCTGGGGCTCTTCCAGACTCATGAGCAAATAACCTAGCCATCCCTGCACTG
CAAATTAAAAGGGGTCGCCAGCCCTTTGACATTTATACAGCTTGACCGAAGATAAATAAA
CTCTCCTGTTCGTTTAAGGAAAGGCCTTCAAAGCCCAGAGCCCTTGGAAGAGTGCTTCTT
CCTTCCACTTAGAGAAATTGACTCTCCCTCTGCGCCCTTGGTGCCTGGCCCGGGGGACAG
GCCGAGGGCAATGCCCAGACTACTCCTGTCCGTGTGCGGGGCCCATACCCTCCTTGCCAC
TGTCCTGTCTGTGCTCCAAATATTAAGAGGATGCCCCATCACCTGGGAGGACGTGCCTCT
GCCCTCCAGCTCCGCGTGGCAGTATTCTGCACAGAGCTAGCAACTCCTCAGTACAACAGG
CGCTTGCAGGGAAACCACAGTCCCTGCACTGTACAGGAGGCCCCTGTGCACA

The following amino acid sequence <SEQ ID NO. 158> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 38:

VHR GLLYSAGTVV SLQAPVVLRS C*LCAEYCHA
ELEGRGTSSQ VMGHPLNIWS TDRTVARRVW APHTDRSSLG IALGLSPGPG
TKGAEGESIS LSGRKKHSSK GSGL*RPFLK RTGEFIYLRS SCINVKGLAT
PFNLQCRDG* VICS*VWKSP RGEG*ALCLS VHIIQTE*MA HDGCH*VTPG
TT*VASTLSS TQHTTPPTVS LFLPLPPLAC LPFS

ENSDOCID <WO 0166751A2 I >

The following DNA sequence Seq-2258 <SEQ ID NO. 39> was identified in *H. sapiens*:

ATAAGGGATACTCGACCCATAGTGATCTTTAAATTTGATCACCTGATAAAATTGGGATTA
CTGGGATCTCTACTGTAAAGTTACCATTTTTCTCTTTGTAACTAATAAGTATCAAAGGGG
ATATACTTTGAGATTATGTGAGTATCACTTTTCTCGCCACGCTTTTGCCCACTCATTTCA
GCATCCATTGATTTTTGCCTAAAGCACTTACTACTCTGGTGTTTGCCTATTTCCATCATC
CCTTCTACATTTAATGATCAGAATTCTACCGTAAAGAAGTGCTTTCCCCACTCTTCAATT
TATTTATGTAATTATTTACTCATGCATGCCAGTGTGGACTTCCGGATACTGATTTTTTAT
TCTATGCGTTGTAATGCATTACTATCATTATTTATTTTGTTGCCCAGCTTGGCCCAGATT
TGGCCACTGAGGGCTCCTTCAGGCTGGTTCCTATGTCCTTCTGGCATGCCCTTCCTCTTC
CCCCCAGCCAAGTAATTTACTT

The following amino acid sequence <SEQ ID NO. 159> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 39:

*GI LDP**SLNLI T**NWDYWDL YCKVTIFLFV
TNKYQRGYTL RLCEYHFSRH AFAHSFQHPL IFA*STYYSG VCLFPSSLLH
LMIRILP*RS AFPTLQFIYV IIYSCMPVWT SGY*FFILCV VMHYYHYLFC
CPAWPRFGH* GLLQAGSYVL LACPSSSPQP SNLL

The following DNA sequence Seq-2259 <SEQ ID NO. 40> was identified in *H. sapiens*:

GAGGGCTCAGAAGACAAAAAGATCTGGAAAAGTTAGGAACTTCCCAGAGACTTGTTGAAT
GGCTTTTACCAAAATGCTGATTGTGATATGGACAATAAGGTCCAGGCTGAGGTGGTCTCA
GATGGAGATGAGAAAACTTATTGGGAAACTAGAGTAAAGGTCACTCTTGCTATGCAAAGA
GACTGGCAGCATTTTTGCCCCTGCCCTAGAGATCTGTGGGAACTTTGAAACTGAGCGTGA
TGATTTAGTGTATTCTGGTGGAAGAAATTTCTTAAGTGTCAAAGCATTTGAGAGGAAGCA
GAGCATAAAAGTTTGGAAAAACTTGCAGCCTAAAAATGTGATAAAAAAGAAAACCCCATT
TTCTGGGGGGAAATTCAAGCCAGCTACAGAAATTTTGCATGAGCAACAAGGAGCCAAATG
TTAATCACCAAGACAATGGGGAAAATGTCTCCAGGGCATGGCAGAGACCTTTACAGCAGC
CCCTCCCATCACAGGCCAGAGGCCTAGTAGAAAATATTGGTTGTGTGGGCTGGGCCCCGG
GCCCTCCTGCTATATGCAGCCTAAGCATTTTTGCCCTGCATCCCACCTGCTG

The following amino acid sequence <SEQ ID NO. 160> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 40:

QQVGCRAKML
RLHIAGGPGA QPTQPIFSTR PLACDGRGCC KGLCHALETF SPLSW*LTFG
SLLLMQNFCS WLEFPPRKWG FLFYHIFRLQ VFPNFYALLP LKCFDT*EIS
STRIH*IITL SFKVPTDL*G RGKNAASLFA *QE*PLL*FP NKFSHLHLRP
PQPGPYCPYH NQHFGKSHST SLWEVPNFSR SFCLLSP

The following DNA sequence Seq-2260 <SEQ ID NO. 41> was identified in *H. sapiens*:

CCCTTGCCTGCTTAAAACCCTCCAGGGGCTGCCGGTTGCTCTGAGAATCCAGTACAGGTC
CCTGCCTGGGGAACCACAAGGCTCTGCCTGATCTGGCCCTGCCTGCTGTCTCTCCTGTCA
CTCTGGGCCCCACCTGTAAAGGGTGCTTTTTGGTTCCTCTGTGTCCTTTTCACATTCTGT

BNSDOCID <WO__ 0166751A2_L>

TCCCTCTTCCTACACACTGTTCCCTCTGCCTGCTCTCCCTTCTTCTCCTTCTTCCCATGA
ATTTGGACTGCCTGCTTGTCCTTCAGAATCTTTGTTGCCCTACACCTTCAAGTTGTTGCT
CAAATGTTACCTTTTCATTGAAATGATCTCTGATTTTCTTTATTATTATTATCATTATTT
TTTTGAGACATGGTCTCACTCTCTCG

The following amino acid sequence <SEQ ID NO. 161> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 41:

PC LLKTLQGLPV ALRIQYRSLP
CEPQCCA*SC PACCLSCHSG PHL*RVLFGS SVSFSHSVPS SYTLFPLPAL
PSSPSSHEFG LPACPSESLL PYTFKLLLKC YLFIEMISDF LYYYYHYFFE
TWSHSL

The following DNA sequence Seq-2261 SEQ ID NO. 42> was identified in *H. sapiens*:

CCCTTGGATATAAGCACTCTCTGCCTGGACACACCCGCTCCTTCTAGTGACCCTGACATT
CCCCTCTCTGACCGGTCAGTCTGCATGTTACCTCTTCTCTCCCTGGACAGCCTGCCCACC
TGGCTGGCCCTTCAGGTGGTCTCAGGTCCCACCTTCTGTCATTCCCAGTGGCATTCAGGC
TTTGGATGCACTATAGGGTGGCTATCTGTGCACTG

The following amino acid sequence <SEQ ID NO. 162> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 42:

PWI*ALSAW THPLLLVTLT FPSLTGQSAC
YLFSFWTACP PGWPFRWSQV PPSVIPSGIQ ALDAL*GGYL CT

The following DNA sequence Seq-2262 <SEQ ID NO. 43> was identified in *H. sapiens*:

ACTGTTTCTACATAAAAATAGCTTCTGTGTTGTCAAAGCACCATGCTTTGACAAGCAACA
AAAACATTTTCAGAAACCTCTTTCAAATAATTCTGTTTCACAAGGCAACAGAATTATAAA
GTCAACTAATGCTGCCACCATTTTATTCAATGTTCCCTTTTCCTGTGTCTTTTTTATGAC
CTGTCTGGGCATTATCTATCTTAGTTGGTCATGCAATAGCATATGTATTCACCTTAACAG
ACTAACTTGGAGGGTTTTTATTTTCTCTCTTTCAACATGTACATTTCACTGATGACCATG
TTGCCTGTAAACTGCTAGGAGCTCAGGTGAAAAGAGAGAGTTATGAGATACAGATTTCTG
AGAGGTGAGGGGCAAGGGTTAATTGAAATTTTTAAAATGATCAAGGGAAGTAGGTTATGT
ATCAACAAACATATTGTTTTTCCAATAACAAATGTCACATTTAAGAACAACAAAATGAGA
TAACCCTAAGCATTCTTTGTATCTATTCACTTCTCTCTTCAAAGTAATCAGAATTAAGTA
ATGTGAGGTCTCCAGTAGCTCATGTAGTAGATTATAACTAGTCCATCTACAATATAAAAG
CTAAAGGATAAAATCCAACCACAAAGTGATACAGGACTGCTAGG

The following amino acid sequence <SEQ ID NO. 163> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 43:

LFLHKN SFCVVKAPCF DKQQKHFQKP LSNNSVSQGN
RIIKSTNAAT ILFNVPFSCV FFMTCLGIIY LSWSCNSICI HLNRLTWRVF
IFSLSTCTFH **PCCL*TAR SSGEKREL*D TDF*EVRGKG *LKFLK*SRE
VGYVSTNILF FQ*QMSHLRT TK*DNPKHSL YLFTSLFKVI RIK*CEVSSS
SCSRL*LVHL QYKS*RIKSN HKVIQDC*

ENSDOCID <WO 0166751A2 I >

The following DNA sequence Seq-2263 <SEQ ID NO. 44> was identified in *H. sapiens*:

AGCTGAGACGTGCCTTGCACTCCAGCCTGGGCAACAAGAGTGAAACTCCATCTCAAAAAA
AAAAAAAAAAAGAAGAGAAGCTTTTTCTGTATTTTCTACCAAAAAGATTGCATCTTTCTT
TTTTGTTGCTTAATGGATTTCATATATAACCTGACCATTGTATAAATTTGGGTCTGGCCA
CGTTCAAATGTAAATACAATTTAAAATATTAATTCCATTTTTAAGCTAATACCAGAAATA
CTTATAGATACTCAGTAATCTGTATGGTCATATTTTATGGAAGGGTAAATGTACATTGAT
TCCCTCCATCTATATTATTGATGATTTTTTTGGTGTCTGTCCAAGAAACACTGTTTGCTA
TATAGTAGGCAGAAGCAGTAGAATGAGTAAGACAGCTTCCGATCCATTTGTTTAGATACT
TCTGAAACCACTGCTCATTTACATGTTTCTCTTTAAATTTCTGGAGATAAATCAGATGTA
TATATTTGAAATACCTTTTCTGAAAATAATTTTCTAGTTTAATAATTATAATTATAAATG
GCATTGCTGTGTAACGTAGTGCTCCTGAG

The following amino acid sequence <SEQ ID NO. 164> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 44:

A ETCLALQPGQ
QE*NSISKKK KKRREAFSVF STKKIASFFF VA*WISYIT* PLYKFGSGHV
QM*IQFKILI PFLS*YQKYL *ILSNLYGHI LWKGKCTLIP SIYIIDDFFG
VCPRNTVCYI VGRSSRMSKT ASDPFV*ILL KPLLIYMFLF KFLEINQMYI
FEIPFLKIIF *FNNYNYKWH CCVT*CS*

The following DNA sequence Seq-2264 <SEQ ID NO. 45> was identified in *H. sapiens*:

TCATATTTAGAGAATTTTCAATCAAATGATTCTGTCAATTCCTAAATATGCTGATAGCAA
CAAAGAAACAGATGTTTGGTTTTATTCCATTGCCAGTGATATGGGAAAAAAAAGCTATTA
ATAAGCATAAATTCTACTAAAGTTGAAAGACATGGAATATTCATATAAATGGAGTACATT
TTACCACTTTTTATACTCAAGAAAATAACATGAAAAATAACTGTACAGGGTACTAGGCTT
AATACCCAGATAGTGAAATAATCTGCACAACAAACTCCCATGACACAAATTTACCTCTGC
AACGAACCTGCACATGCACCCCAAACTTAAAATAAAAATTAAAAAAGAAAAAAATAGTTA
TATAGTAAAGAAAAAGTAGTAAGTGTCAGCGGGAGACTTCAAAATTATGAACAAAGTAAA
AGAGGAACGAGGGTGGGGTGTCAGATCTAAATAAAAGAAATACAAAAAA

The following amino acid sequence <SEQ ID NO. 165> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 45:

F CISFI*I*HP TLVPLLLCS*
F*SLPLTLTT FSLLYNYFFL F*FLF*VWGA CAGSLQR*IC VMGVCCADYF
TIWVLSLVPC TVIFHVIFLS IKSGKMYSIY MNIPCLSTLV EFMLINSFFF
PYHWQWNKTK HLFLCCYQHI *ELTESFD*K FSKY

The following DNA sequence Seq-2265 <SEQ ID NO. 46> was identified in *H. sapiens*:

GCAACACTACAAAAACAGACCAAAAAACTGAAGGACTTTTACAGCACTCATTTCCAGCCA
GAGGAAACTAGAAACGTTTGGTGGAAGAGGTGTCCTTTGAGCTGGCCCTTGAGGACTCTA

BNSDOCID <WO 0166751A2 I >

ATAGGGGATGAATAACTGTAGAAAGCTGGATTATTCCAGGAGGCAGAAGGCACGGGGGCA
AAAACATAGAGGTAGGAGAGCCTACGTTTTGCAAAGGAAGAATGATCAGTAATCTATTTT
GGTGACAGCCTAGAAAAAATATGGTGGAGTGGTGGGAAAAATGGGTTGGAATTAGGTTGG
AACCAAATGGTAACACACAGGTCTGGAATGTGACTTTAAGAAGTTTAGAATATTTGATAG
GTACCATTGACCTACTGAAAAGCATTTGAGGAAGAAGGGCTTAATCAAAACCATGCTTTA
GTGTGAACAAACAAACAATAATCAGGGATATGTGACAACAAATATTTGATAAAATCTAAT
GTCAGGAAATATTCTTGTTGTAACATAAGGAGAAAACTAGTAGGCTGTTGAAGTTTGATC
CCCTGGAAGAAATAATAAGAAAAATAAAATAATAAATTATAATAATAGCCAACCTTTGTT
AAACTCATATTATGCACCAGGCTCTGTCTCCAAGTTCCTTATAATAACAATCGA

The following amino acid sequence <SEQ ID NO. 166> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 46:

SIVIIRNL ETEPGA*YEF NKGWLLL*FI ILFFLLFLPG DQTSTAY*FS
PYVTTRIFPD IRFYQIFVVT YP*LLFVCSH *SMVLIKPFF LKCFSVGQWY
LSNILNFLKS HSRPVCYHLV PT*FQPIFPT TPPYFF*AVT KIDY*SFFLC
KT*ALLPLCF CPRAFCLLE* SSFLQLFIPY *SPQGPAQRT PLPPNVSSFL
WLEMSAVKVL QFFGLFL*CC

The following DNA sequence Seq-2266 <SEQ ID NO. 47> was identified in *H. sapiens*:

CAATATATTTTTCCATCATACAAACAAAAGACCCTTGACTCCACACTCTTTACATTATCT
TCAGTGGCTGCCTTATTTCTTCACATCACTTCATAGGGAAATAAAAATAAAATAAAATAA
AAATGGAAAAAAAATCTCTTCAAATAATTATTTTTGGTAGCCTTCACATTTTCTTTCAAAC
TTCATTCCTATGAGGTCTTTATCCTCAGCAAGGAAGCAAAGCTATTCAAAAGTCATCAAT
AATTAATTACAAAACCTCATTTTATCCCATCTAGTAGTAGCATTTAACCCAGCTGATTAT
AAATTCCTTCTTCCATGGTTTCTTTACTTGGACTTCTGGGCACCACACTCTCTTGGATCT
TATTCTGCCTCCCTGCCTTGTCTTCTTCATATCTGTTATGCATTTTCTGCATTCACCCAG
GCTCTACTCTCTTGAGTGCCCTTGGACTCAATTCCTGTGCATTTCTCCATCTATTTCCTT
TAACGGCATCTATATACTGATGACTCAGAAGGGTAAATCTCCAGATATTCCTCTGAAATC
TGGGATCTATCATCTCTACTTGGATGAGTTGGGTACTCCACATCCTCACTGGAATCTCCT
CCTGCAGAGATTATTCTACACACAGG

The following amino acid sequence <SEQ ID NO. 167> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 47:

IYFS IIQTKDP*LH TLYIIFSGCL ISSHHFIGK
K*NKIKMEKN LFK*LFLVAF TFSFKLHSYE VFILSKEAKL FKSHQ*LITK
PHFIPSSSSI *PS*L*IPSS MVSLLGLLGT TLSWILFCLP ALSSSYLLCI
FCIHPGSTLL SALGLNSCAF LHLFPLTASI Y**LRRVNLQ IFL*NLGSII
STWMSWVLHI LTGISSCRDY STHR

The following DNA sequence Seq-2267 <SEQ ID NO. 48> was identified in *H. sapiens*:

CTTCTGTCTGGTTTTAATGTGAACATATTTCCTTTTCAATCATAGGCCTCATATAGCCCC
AAATATACACTTGCAGATACTACAAAAAAAACTGTTTCAAACTGCTCTCTCGAAAGGAAT
GTTCAACTCTGTGAGTTGAATGCACACATCACAAAGCAGTTTCTGAGAATGCTTCTGTCT
AGTTTGTATGTGAAGATATCCCTTTTACCACCAATTCCTGAAAGAGCTTCCTATATCCAT

BNSDOCID <WO 0166751A2_I>

AAGCAGATTCTACAAAAGATGTGTTTCAAAACAGCTCTACCAAAAGAAAGGTTCAACTCT
GTGAATTGAACACACACATCACAAAGGAGTTTCTGAGAATGCTTCTGTCTAGTTTTTATG
TGAAGATATGTACTTTTTCCACAATAGGCAACAAAGTGCTCCACATGAACACTTGCAGAT
TCTACAAAAAGGGTGTTTCAACACTAGTCTATCAAAAGAAAGTTTCAAGTCTGTGAGTTG
AATGTATACATCACAAAGCAGTTTCTGAGAATGCTTCTGGCTAGTTTTTATGGGAAGATA
TTTCCTTTTCCATCTTAGGCCTCAATCGCTCAAATATCCACTTGCAGGTACTACAAAAAC
ACTGAC

The following amino acid sequence <SEQ ID NO. 168> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 48:

SVWF*CE HISFSIIGLI *PQIYTCRYY KKNCFKLLSR KECSTL*VEC
THHKAVSENA SV*FVCEDIP FTTNS*KSFL YP*ADSTKDV FQNSSTKRKV
QLCELNTHIT KEFLRMLLSS FYVKICTFST IGNKVLHMNT CRFYKKGVST
LVYQKKVSSL *VECIHHKAV SENASG*FLW EDISFSILGL NRSNIHLQVL
QKH*

The following DNA sequence Seq-2268 <SEQ ID NO: 49> was identified in *H. sapiens*:
ACTTAACAAAACCTTCAGCGTCTGCTCATCACCACATAATAAAACCCAAAAGTTATCACT
AATCCACCTTCACTCACCTCCGTTCTGTTTGTGCTCCAACATTTTTTCTATTTCTTCAAC
TATAATGGGTGCTTTCATGTGTCCCTGCATTTGTATATGTTGATTGTTCTGACTGAAGGC
CCCTCCCTTACCTTTCATTCATGCTGGGAAATTCATGCTAGCTCTACTGAAATCATTTTC
CTTACTTCCTTGAGTAGAATGAATTGGCTCTTCATTTGCACCCCCACAGAACATTTTCTA
AATTTAAAAAAATAGCACTATTTGAAAACTGAGAAATGGCGCCCGATATTCAGGATACACA
GCAATGCCTGGAACAGTTACGATGAGTAATTGTTTAAATTTAACAAACACTGATATAGTA
CTTATATTCAAGGTTCTGTTGTAAGTGTTTTACAAAGATCAACTCATTTAATCTTCATGG
AAACTCATGAAATAAGTACTATTAGTATTCCCACCTAATAGA

The following amino acid sequence <SEQ ID NO. 169> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 49:

T*QNLQRLLI TT**NPKVIT NPPSLTSVLF VLQHFFYFFN YNGCFHVSLH
LYMLIVLTEG PSLTFHSCWE IHASSTEIIF LTSLSRMNWL FICTPTEHFL
NLKNSTI*KL RNGARYSGYT AMPGTVTMSN CLNLTNTDIV LIFKVLL*VF
YKDQLI*SSW KLMK*VLLVF PPNR

The following DNA sequence Seq-2269 <SEQ ID NO. 50> was identified in *H. sapiens*:

CAATACATCAGGTGCTGCCGGCTTCCCAAGCTTAGTGGCTTCACACAAAACCCTAGTATT
GCTCACAACTCTGTGTGCAGGAACTGGGGACTCAGCAAGGTCAGCTTGCGACCGCTCTAC
CTGCCCGCTGGTCTCCCTCTGAGACTTCCATCCTCAGGAGGCCGGGCTGGGTCGGAGGTC
CGAGGTGGCTGCCCTCCTCCACCAGGGACCCCAGGGCTCTTGCACACATGTCTCTCTCCA
AAGCAGGGCTGCTTGAGATTGGGCTCCGGCTCACAGATCTGTGGGGTCCTGGAGGCCTTG
TAAGAACACTGGCTTTTGCTCTGAGCAAGAGGGTCCCAGAGTACAAAAGCACAAAGGCAG
CTGCACTGAGCGGGAAGGGGCGCAGGTAGACTCCGATGGTGGCTGGGACCAGGGGTGGTC
AGATTCTGCCTCCATCCTGCAGGGTAAGGGGACAGGGCCTGCTGCTAGATGGGGCTTCTG
GCCTGGGAGC

ENSDOCID <WO 0166751A2_I>

The following amino acid sequence <SEQ ID NO. 170> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 50:

QYIRCCRLPK LSGFTQNPSI AHNSVCRNWG LSKVSLRPLY LPAGLPLRLP
SSGGRAGSEV RGGCPPPPGT PGLLHTCLSP KQGCLRLGSG SQICGVLEAL
*EHWLLL*AR GSQSTKAQRQ LH*AGRGAGR LRWWLGPGVV RFCLHPAG*G
DRACC*MGLL AWE

The following DNA sequence Seq-2270 <SEQ ID NO. 51> was identified in *H. sapiens*:

TTGAAATCCAAAAGTAGTTTTTTTTTAGTTTTCTGTCACAACTTCGTTCTTGGGAGTTTG
CTCCTTGCCAACTAGAAACTATGATTTTCAAGAGAATACAAGCCCTCTTAACAATCAGAC
AGGATTATTATATCTCTGTGTCGATGCGGATTGAAGCCCCACAAAAGCATCAATTTTTGA
CTTCAGTTCAAGATATGGAACCCCTGCTTTTCTACTTAAGATTTTATTTTTCTTGAAGAA
CTTCTAGAAGTTCTTTTTCGTGAAGATTTTATTTTGAAGAACTTCTGGAACATTCCTATT
TAGCTGTTTTTAGGAGAGAAGCCAACTTTCATTTATTTGGTGAAAGAAGATGGGCTTTAA
ACACATTTCAATTTGAGGATGGGGTCCTACTGGAAATAGTTTTGCAAGTAGCTATTTACA
AAATGTTTCATTGTGGTAATAAAGAGAAAGGGAGTGTGAGGAGAACTGGGTTCTTGTCTT
GGCTCTCTGCTAACTACCTCTATGGCTTTGGGGAAGTCATTTTATGTCTAAGCCAGCTTT
CTTTCAGTGCACCTCTGGGAAGACAGGGGTATAAGTTATCCTACTCTCAAAGATGCTTGA
GCCCACTGGTGTATTATACATCATGCAATTTATTCAAGAAGG

The following amino acid sequence <SEQ ID NO. 171> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 51:

EIQ K*FFFSFLSQ LRSWEFAPCQ
LETMIFKRIQ ALLTIRQDYY ISVSMRIEAP QKHQFLTSVQ DMEPLLFYLR
FYFS*RTSRS SFS*RFYFEE LLEHSYLAVF RREANFHLFG ERRWALNTFQ
FEDGVLLEIV LQVAIYKMFH CGNKEKGSVR RTGFLSWLSA NYLYGFGEVI
LCLSQLSFSA PLGRQGYKLS YSQRCLSPLV YYTSCNLFKK

The following DNA sequence Seq-2271 SEQ ID NO. 52> was identified in *H. sapiens*:

ACCCAGTAATTTGTTTTCAAAACTGTGACATTCTCATTCTATAATACCTAAATTCACAGG
ACAAAAAATACCAAAGGGCTGTGTGTGCATGTGTCCTGGATTACTTCTGCAGTGATTTGG
TGTTCTGCTTCCCTCTGCTGGGTAAAAATGGTACAGCAAAATTTCTGGAAAAGAAAACAA
CCAATTACATACCTGCAGGTTTTGCAGGTACTTGGGGGTGTGGTGAGCACGTGAATATGG
CCAGGGGGTGTCCCTCAGTCAGAGTGCTCTCTAGCATTCCTTTCCATCACTCCATGGCCT
CTGAAATATTTTATCTAAAAAGAGGGCCCAGGCATCCACTTCGATCTTTGCAAAGTATGG
GAAAAGGAGAAACATCCAGTGATTAGATTTAGGATCCACAGGAGATCTTCATTTGACACA
AA

The following amino acid sequence <SEQ ID NO. 172> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 52:

TQ*FVFKTVT FSFYNT*IHR TKNTKGLCVH VSWITSAVIW CSASLCWVKM
VQQNFWKRKQ PITYLQVLQV LGGVVST*IW PGGVPQSECS LAFLSITPWP
LKYFI*KEGP GIHFDLCKVW EKEKHPVIRF RIHRRSSFDT

ENSDOCID <WO 0166751A2_I_>

The following DNA sequence Seq-2272 <SEQ ID NO. 53> was identified in *H. sapiens*:

ATTAAAGAATATACACTATCAAAAAAAAACCAGATTTGGAAATGAACCAAAAAAAATACT
TTTAGAAAAGAAAAATAATAATCATTGCAGTTTAAAAGTCAACAAGCATTTCAGAGAGCA
GATCAGAACCAGCTGAAAAGAACATTCAGTCTACAAAATTGGCCAGAGTGGCACAGAGGT
GAGGAGGTGGAGCTGAAGACAGGGCAATAGAGAGGAGTCCCCCCAGGAGGATGTGCTGCG
GGGTAGTTGTCAAGAGGGAGTTAAGAGGCTTACCAGAAGGTGAAGAAACCTCAGATTTTG
AAATGGAGCAAGTTCTGAACAAAATAAATAAAATGAATTCCCCACCTGAGAGAAACTACA
GTGTGCCACAGACAGTCCTGCTTATTGAGGAAGACACTCATGTTTGCTTTGTGGCTTTCT
GTGGCCCTTATCTCTCATGTAGTGCATACCCTGAATGAGAAGCCAGGAGGATAGCCCTTA
GATTGGCTTCTGGAGACAGAATCTTGACTGTATATCCTGGGTCCTGGTG

The following amino acid sequence <SEQ ID NO. 173> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 53:

*RIYTIKK KPDLEMNQKK YF*KRKIIII AV*KSTSISE SRSEPAEKNI
QSTKLARVAQ R*GGGAEDRA IERSPPRRMC CGVVVKRELR GLPEGEETSD
FEMEQVLNKI NKMNSPPERN YSVPQTVLLI EEDTHVCFVA FCGPYLSCSA
YPE*EARRIA LRLASGDRIL TVYPGSW

The following DNA sequence Seq-2273 <SEQ ID NO. 54> was identified in *H. sapiens*:

CTACAGTCACATCGTACGTTACAGTTTTTACAAAATACTCTTATATACCATCTGATTTAA
TGCCACCAACAACTGTACAAGGTGTTGTCACAATCACTTAGTGACAGACAGGGATTGATA
TGATGGCTACAAAAAAAAAAGGCAATAATGAAACTTAAACTCAGTCTTCTGATCCAAGCTC
TGGGGTTTTGCCATGAATCAGCAGCTGCCAGGGACCAAAACCAGAGGCAGAGGTAGAAAA
GTAAACATGAAATAGGCAGGAACTGTACACTGTGCAGTTTAGAGTCACACATCCTCACAC
GTCTGTTAGAGTAAGAAGTGCACCAGCACCTCTTAAACTTTTACATCAATTGTATCTTCA
TGGCAGAAGGCAGCCTTTCTGTTAAATCTGGGAATTTATCAGAAAGAGGACAACCCAAGC
CTCATTTCAGAGAGAAGTCTGGTATACTCTTAGAAATCTATGTGACTGTCACCCCTAAGT
ATATTATTTTTTCTCTTTCA

The following amino acid sequence <SEQ ID NO. 174> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 54:

EREKII YLGVTVT*IS KSIPDFSLK* GLGCPLSDKF
PDLTERLPSA MKIQLM*KFK RCWCTSYSNR RVRMCDSKLH SVQFLPISCL
LFYLCLWFWS LAAADSWQNP RAWIRRLSLS FIIAFFFVAI ISIPVCH*VI
VTTPCTVVGG IKSDGI*EYF VKTVTYDVTV

The following DNA sequence Seq-2274 <SEQ ID NO. 55> was identified in *H. sapiens*:

AGATGGATAGATAGATAGATAGACAGATAGATAGAATTAGAAAATACATATCTGTAGTAG
TTTTCTCTAGGAGGGATTGTGGGACTTTTGTGGGGATTTCCCTTTGCTCTTTTGTTTCTG
GACAATTTCTACACTTTTTCATGTATATTCTTAACCAAATTCAGTTTAAGATTTCTGCAA

BNSDOCID <WO__0166751A2_I_>

GTCTTTCTCTTTTTAAGTAATTCTTTTCCTAATACGAGAAATTCACAATGTTCATGGTAT
GTGTGTGTGTCTGTGTGTCTGTTGCATGTGTCTGTTGTTTGTGTGTCTGTTGTGTGTGTC
TATTGCATGTGTCTGTATGTTGTGTGTGTACTTGCTTGGACCCATTGGCACCAAGCTTTC
TGATTCTTCTTCATCTTCCCCAGCTTCCTCTCTTCCCAGAAAATACACTAGAAACTTATC
TTTGAGGGAAGAAGGCAAGCCTATTATAACCTTCTGCCCACATTCCCTTATCTAAACATG
GTTATTGGCTACTGGTTACTTATTACATTGAACAGTGAGCACTAATTTATACATTCAAAA
CCTGCATCCTAAGCTCTCTTAAAAAACATGATT

The following amino acid sequence <SEQ ID NO. 175> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 55:

RWIDR*IDR* IELENTYL** FSLGGIVGLL WGFPFALLFL DNFYTFSCIF
LTKFSLRFLQ VFLFLSNSFP NTRNSQCSWY VCVSVCLLHV SVVCVSVVCV
YCMCLYVVCV LAWTHWHQAF *FFFIFPSFL SSQKIH*KLI FEGRRQAYYN
LLPTFPYLNM VIGYWLLITL NSEH*FIHSK PAS*ALLKNM I

The following DNA sequence Seq-2275 <SEQ ID NO. 56> was identified in *H. sapiens*:

TATTACATTGAAAACAAACATCTTCCTTTAAGCTTCTTGTTCCAGCTCTCATCAAATCTA
TTTTCTTCCAGAGCCAGGCTTCTCCAAAGAATTATCTACATATAGTGTCTTCTTCACCTT
TTATTCATTTCTTTATCTCACTCCAATATGGCTTCTGCACTCATCACTCTACCAAAAGTG
TCTTTACTGAGGTCATCACTGCCCTCTATGTTATCAGATACAATGAACCCGTCTTTGTCC
TCAGCTTACTCCTCCCCTCAACAGTCTTCAGCATAGTTTACTAAGTTCTCCTTCTTAAAA
CATTCTCCTCTCCCTACCTGCATGAACCTATACACTCAGGGTTTTTCTCCTACCTCTCTA
TCACCTCCTCATTTGCTGGTTATTTTTCTTCTACATGATCTCAAAAAGAGGAATTCTCAG
GGCTCCATTCTGGGTTCTCTTCTCCGTCTGGACTGTTCCTCTACATGATTTTACCCACTC
TCATGCTTTTAAATGCCACCTACATGCTGATGGCATCTAAATTTGTATTTCTAGCCTAGA
TGTCTCTTCTGAGTTCCAGATCAGTATATTTAACTACCTACTTGACAGCCACTGCCATAT
TGGAATACTCTTGCACAAAGGTGAT

The following amino acid sequence <SEQ ID NO. 176> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 56:

IT LKTNIFL*AS CSSSHQIYFL PEPGFSKELS TYSVFFTFYS
FLYLTPIWLL HSSLYQKCLY *GHHCPLCYQ IQ*TRLCPQL TPPLNSLQHS
LLSSPS*NIL LSLPA*TYTL RVFLLPLYHL LICWLFFFYM ISKRGILRAP
FWVLFSVWTV PLHDFTHSHA FKCHLHADGI *ICISSLDVS SEFQISIFNY
LLDSHCHIGI LLHKGD

The following DNA sequence Seq-2276 <SEQ ID NO. 57> was identified in *H. sapiens*:

TTGAGCAATAAGTAGCTTCTCTTGTTGCTTCTTTGGGATATATCTTTTTACCTCTGGCTG
CTTTAAAGATTTTTTTTTTCTCTGTTGTATATTCTGTCCTATTGATTGGTACTCCATCTA
TACACATGTTGGATCTTTTCACTGTCCCACGTTTCTGATGCCATTATTGTATTTTTCAAC
GTTTTGTTGTGGTTAATCTTTGTATTTCAGTGTGCTTAGTTTCTACTTACCTGTTTATTA
AAAACCTTTCATCCTGCTAGTAAATGACTCTCATGAATTCTTAATTTCAGTTATGATTTT
ATTATTTATTTTAGGTTTGTTTTTTTTTTTTTTTTTTTTTTTTGCCTGTTTGTTTGAGAT
GGAGTCTCGC

BNSDOCID <WO 0166751A2_I_>

The following amino acid sequence <SEQ ID NO. 177> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 57:

*AISSFS CCFFGIYLFT SGCFKDFFFL
CCIFCPIDWY SIYTHVGSFH CPTFLMPLLY FSTFCCG*SL YFSVLSFYLP
VY*KPFILLV NDSHEFLISV MILLFILGLF FFFFFFFACL FEMESR

The following DNA sequence Seq-2277 <SEQ ID NO. 58> was identified in *H. sapiens*:

ATATGCCAGATTCCTTCTGCCCAGCTCCCCACCTTTTCCCAGTTAGTTTCTCTTATGAGA
GTGCTCACCTGAGGTAATGTGATTTATAAAGGTGACCCATGGCCACAGTCGTGAGTGGTC
TGAGGAACAATCATAGCACACTGCTCTCTCCTCCCACTCCCTATGCCATTGTATTCATGC
ACCAACCTAATAACTAAGAGATTGACCTTTCCCTGATGCAGCCCTAGTTTCCGTCTCAAG
ACGCTTCCCACTTTGCTCAGAGTCCAGTAAGAAACACAGACAAGTAAGGTGAAAATTAAA
ATGCCATATGGTGAGTTGCTAAATGCTACCACAGGAATATGCACTAGGCACTTTGAAAGC
ACAGAGGAAATAAAGCAAACTCAGCCTTGAGGCGTGTGGAGTTTAACCAGGTGAAAGCCA
AGTGAACAGGCAGGGTAATCAGGAAGAAAACACATGGACCT

The following amino acid sequence <SEQ ID NO. 178> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 58:

R SMCFLPDYPA CSLGFHLVKL HTPQG*VCFI SSVLSKCLVH
IPVVAFSNSP YGILIFTLLV CVSYWTLSKV GSVLRRKLGL HQGKVNLLVI
RLVHEYNGIG SGRREQCAMI VPQTTHDCGH GSPL*ITLPQ VSTLIRETNW
EKVGSWAEGI WH

The following DNA sequence Seq-2278 <SEQ ID NO. 59> was identified in *H. sapiens*:

TAATTTATTTTCTTATTAAGTAACTCCATAATCTGTTCATAGTCTACATTCAGGTATGTG
CAAACATGAGATATTTTGTATTCCCTCTGACACTGTAAAAGTTTTCAGTAGTTCTCCAAA
TACCCCTTTTGGTTTTGTGCTTTTAAAATACACCATCTGACATCCTTTTGCAGTATCTCA
GAAAATTTCAAAGCGTTATTCGAATCCAGATACCATATGACCGCACACCTCAGAGAGTCT
ACCTTGATGCCTCTAATCTCCTTGAAGTATTCTATCCATAAATATTTTAGAAATTTAGTT
ATTGAAATTTAGTTATTAAAATTTATCCTATACTAGGCACTGACATCCTTAATCTCAATG
ACCCATTGTAATTATCTTTTAGCTCTGAAGCTCCAACATAACAAAACATATATTTATAAA
TTAGAATTAAGAACAGAAACTAAGAATCAATCTAAAATCACTTCAGTGATAATTTTTCTG
ACAATTGCATCACAATTCTTTACTATTGTGGTTTTTAGGCTTACTACATCTTTCCATAAT
GCTGAGTTTTATTTTCTGAATTAAGCTCAAATATCTGAGATGATATTTATATATTTTTTA
TCTTTCATGGGAGCTAGCGTAGTGCTGGGCTCTGAATTTAAATGC

The following amino acid sequence <SEQ ID NO. 179> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 59:

*FIFLLSNSI ICS*STFRYV QT*DILYSL* HCKSFQ*FSK YPFWFCAFKI
HHLTSFCSIS ENFKALFESR YHMTAHLRES TLMPLISLKY SIHKYFRNLV
IEI*LLKFIL Y*ALTSLISM THCNYLLALK LQHNKTYIYK LELRTETKNQ
SKITSVIIFL TIASQFFTIV VFRLTTSFHN AEFYFLN*AQ ISEMIFIYFL

ENSDOCID <WO 0166751A2 I >

SFMGASVVLG SEFKC

The following DNA sequence Seq-2279 <SEQ ID NO. 60> was identified in *H. sapiens*:

TCATTTTCTTATGATTTGCCTTAGCTTCCCCTCCTGTCTAGTCCTACCTTCTACCATGTC
TAAGCATGGGCACCCTTGGTGATGCTCCCGTCTTCTGTGGCAGGACTTTCTAAAAGTTTC
CAGTACAAACTCCAGACTACAATTACTCTCTGCAAACAGCCTGTGTACTTTTAGACTTTC
TGGGATTTCTCATCATTTTGATTAGCCAAAAATCTCTTTGAATTTAGAAAACAAGCTATA
CATTCATATACTTAAAAAATAACTTAAGGCTTAGAGTGGAAGGACAGAAGCTGAGAAAGG
AGAGGATATCATCGTGCAATTAGTGTTCCATCTTGAAAGTGAAAGCCTCCATTTATATTT
TGTGTTGGTTCCCTTTTGTATTGATATTAGGGATACTAAGCAATTGTCACCTACTTTGCA
AATACTTGTTACATGTGCCTTTAAATTTCATTTCAGGTATCTTCAGAGACACAGATGTTT
TACATTTTAATGCGGACAAATCTGTTCATTTTTCACTTTAAGATTTCTGGTTGGTGGGTC
ATGCTCATGAGGCCTTTTTACTCCACAATTTTAAAAGTTTCCTGGATTACCTTCTGAAAT
TTCATGGGTCACTCTTTCATATTTAGATATTTCATGGTCAGATATAGATCTATGAGGACT
TT

The following amino acid sequence <SEQ ID NO. 180> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 60:

IFL*FALASP
PV*SYLLPCL SMGTLGDAPV FCGRTF*KFP VQTPDYNYSL QTACVLLDFL
GFLIILISQK SL*I*KTSYT FIYLKNNLRL RVEGQKLRKE RISSCN*CSI
LKVKASIYIL CWFPFVLILG ILSNCHLLCK YLLHVPLNFI SGIFRDTDVL
HFNADKSVHF SL*DFWLVGH AHEAFLLHNF KSFLDYLLKF HGSLFHI*IF
HGQI*IYEDF

The following DNA sequence Seq-2287 <SEQ ID NO. 61> was identified in *H. sapiens*:

ACCCTTGCCTTGTAGACATCACATGCTAGCAGGTGAGACAAACAACAAACAATAAGTATT
CCCAATAATGTCTGCTATAGAAAGGGTAAAGTGTTATAAAAAAACAAACAAACAAAACAC
TGGTGCTGGGAAGGCTGGCTGGAATTGTAAAAAGGGTGCCACTGAGAAGGTGATATCTGA
GCAGACTAGAAGAAGGTGAGAAGGTAGATTGTGAGGCTGGAGCACATCTAGGGGATGGTG
TTCCGCACAGAGGGAAGAGCTAGTGCAAAGGTCCAGAGAAGGGGAGAGCCTAGGACGTAT
GAGGGAGAGCAAAGAAGCCAGCCTGTGTGCAGGAGCCAACGCGAGCCAGCGTAGAGGCAC
TGAAGCCGGGGATGGCATGGGGGCGGCGGAAAGGCTGTGCCAGTGACTCTGAGTGGTGTG
GGAAGCTATGCAGGCTTTTGAGCAGAGGAGTGACATGAACTGATACTTGGCTTTTATAGT
AATTTAGGTGATGGTGGCTCAGATCAGGGCAGCAGAAGTGGAGGTGGGAGAAGCAGTTGG
TTTTGAACCTAACCTGTTTCCTAGTGGACTAGATGTGGATGGGAGAAAAAGATGGGAGTC
AAGGATGACACCAAGAGTTCTG

The following amino acid sequence <SEQ ID NO. 181> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 61:

QNSWCHP*LP SFSPIHI*ST RKQVRFKTNC
FSHLHFCCPD LSHHHLNYYK SQVSVHVTPL LKSLHSFPHH SESLAQPFRR
PHAIPGFSAS TLARVGSCTQ AGFFALPHTS *ALPFSGPLH *LFPLCGTPS
PRCAPASQST FSPSSSLLRY HLLSGTLFTI PASLPSTSVL FVCFFITLYP

ENSDOCID <WO___0166751A2_I_>

FYSRHYWEYL LFVVCLTC*H VMSTRQG

The following DNA sequence Seq-2288 SEQ ID NO. 62> was identified in *H. sapiens*:

AAGTTTGAAGCTCTGGTAGTTTACAATTTATCAGTGATAGGAACAAAATGTTAGCATAAA
AACTTTGGAAGGCATTAAATATAATGGGAATTAGAGTTTGATTATGTCATGCTAATTTAA
TGAAAATGAATTAGTTTTAAAGAGTTTTAAACATAAGGGAAAATGTGTAACTAATATGAA
ATCCTGTATGTTTATTTGCTTCACTATGGTACAATTTTTACTATGTATTTGTATCCCATA
ACATCACTTTGTATGTCTTCAATATACAAAATAAAATTTATTTAAAATGAACATTTGATG
AGCTCTAATGCGGAAAGACCTGCATAAATTAGTCAGTACTGTCATGACATTCATGGCTCC
CAGCTTCAGGTTTGTTCTCAATTTTCCTCATAATCCTTCTGTTACCATCATCAGCAATTT
CTCTTATTTCACTTTTCAGTTATTTCATAACTGATGCACTATCCTAAAACCTCTGACAAA
TGTTTCCACTAAAACCACACATACACACACACAAAACAGATTGTGACACTCACAATGGTT
TATTGACTATTGTCTTCAAGCATTAGAAAATACATACATGTACTCAGCATTGTGTTCATG
TTCAGAGTCACTGCTGCTCCCTCGGTCTTCATGTAAGAACTCAT

The following amino acid sequence <SEQ ID NO. 182> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 62:

SLKLW* FTIYQ**EQN VSIKTLEGIK YNGN*SLIMS
C*FNENELVL KSFKHKGKCV TNMKSCMFIC FTMVQFLLCI CIP*HHFVCL
QYTK*NLFKM NI**ALMRKD LHKLVSTVMT FMAPSFRFVL NFPHNPSVTI
ISNFSYFTFQ LFHN*CTILK PLTNVSTKTT HTHTQNRL*H SQWFIDYCLQ
ALENTYMYSA LCSCSESLLL PRSSCKNS

The following DNA sequence Seq-2289 <SEQ ID NO. 63> was identified in *H. sapiens*:

CCTGGGTCCCACCCCAGACTACTGAGTCAGGCAGCATCTCTTGACCCAGGAAGCGGTACT
CTTAATAAATCACCTGCAGGTGATTCTTTTCTTCTGCACTTTGAGTTGAGAACCACTGCT
CTAACAGGTGAATAAACATTAATATAACAAATTGCAATACAGTTGTAGGGAAGGAAGATA
AAGGTATGCCACCGATAGAAATACATATAGGGTAGAATTCATTCATCCATGCAACACTTA
TGAAGACCCATTGCATGTCAGGCACTATTCTAGGCACTAATGGCAGAATAGTGAGCCAAG
CAGACAAGGGCCTGGTTTCATGGTGGCGGGGAGGCAGACTAAGTGAATTTATAGCTGTGA
ATTGTGATAAGTGTCTGAAGGAAGACACGAAAGCCAGTGTTATGGGTAGATAGCAACGGC
CAGGAGATGGGCTTCTCAGAGGAGGAGTTTACTCTGAGGATGGAAGAGTGAGAAGAAAGT
CACCTGTGTGCAGTCAAGGGTGGGCACTGGGAAGAACTGTCCAAAGAGAGGGAGCTCATT
TGTGAGAGACTTGCCACAAGGAGGAAAAGAGCTTG

The following amino acid sequence <SEQ ID NO. 183> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 63:

QALFLLV ASLSQMSSLS LDSSSQCPPL
TAHR*LSSHS SILRVNSSSE KPISWPLLST HNTGFRVFLQ TLITIHSYKF
T*SASPPP*N QALVCLAHYS AISA*NSA*H AMGLHKCCMD E*ILPYMYFY
RWHTFIFLPY NCIAICYINV YSPVRAVVLN SKCRRKESPA GDLLRVPLPG
SRDAA*LSSL GWDP

BNSDOCID <WO 0166751A2 >

The following DNA sequence Seq-2290 <SEQ ID NO. 64> was identified in *H. sapiens*:

TCTGGACCTTCCTGGGCTGGGCTCAGATGAGGAATGTGTGTGTGTGTGTGTGTGTGTG
TGTGTGTGTGTGTGTGTGTGTGTGAGAGACAGAGAGAGAGAGAGAGAGTCAGGAAG
TGGGGCCGGGGGGCGGGGGGCAGGGGTTATCTAATAAAATGAGCCAAGCAAGTTTTGTGC
GTAGCTTGAGCTTCTGTCCTCCTCCCAGATAACAGACAAGCTTCCTCCCAGCTGCCCTTT
GTGGGTAACGCTTGTTTTGTGTCTGCCTTGGGGCCTGAATCAAACAGAGTTTGTTTATGC
AGGATGTACAAGGTGTCAAACCCAAACCTTGGTTGTGAGGAAGACGGCCTTCCTGACTGG
GCCAGCTATCTCCAATGACTTGAATAATTGTCCACAGGCTGAGCAGGGCAAACACTTCTG
AAGATATATATGGGCCAGACTTTTGTAAGATTCATTAATGTCTCTTGGCAACTGGCAGGG
GAAAGTATAGAAAAATACATCTGAGCAAGATGATG

The following amino acid sequence <SEQ ID NO. 184> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 64:

IILLRC IFLYFPLPVA
KRH**ILQKS GPYISSEVFA LLSLWTIIQV IGDSWPSQEG RLPHNQGLGL
TPCTSCINKL CLIQAPRQTQ NKRYPQRAAG RKLVCYLGGG QKLKLRTKLA
WLILLDNPCP PPPGPTS*LS LSLSLCLSHT HTHTHTHTHT HTHTFLI*AQ
PRKVQ

The following DNA sequence Seq-2291 <SEQ ID NO. 65> was identified in *H. sapiens*:

CAAAGGAGTGATAATTATATACATAGGCCTGATAATTTTGGGCAATATGGATTTAAGTGT
GTTTATAATATTGATGGTTTGAGATTTTTTTTTTCCAACAGTAAATAGCAATCTGAGAAG
GTGGTGCTCTGAATTGAGTTGTTTGCTTGGCAGATATGGTAGCCGATACAAATGTGGCAG
CAAATGAGGGCTACTGGGTAAGAAAAAAAGTTGAGACAATCAAGCCTGTGATTCCATTAA
AGTAGGGAAGAGCTACTAAGAAGAGGCTTATAGAATGAGGGAATTAGAAATATCAAAAGA
TTATACACCTGTATAACAACAAAGAGTAGAAACAATGAGAATGAGGTGATCAGAAATGGG
TTGACAAGGCTTCATGCTCAGACAGTAAATATTGTTCTGTATGACTTTTTAGGTGGGGCT
TTTCTAGGTCCTGAAGATTTTAGGATATGTGTCTGGAAATAGGTGGATAAAGTACAATCA
AAGAAAACATTGGTTGAAGTAAAATAAATCCAGAATGAGACAGTTACATGGACAGTTAAA
TATCTCATAATTATGATTGAAGTTTTAGTGGAGATAAAAGCTGAGCAACATACTTCTAAA
TGAGTAAGGCTAAGTGACTCAAAGGAGAATAGGTGACTTTAG

The following amino acid sequence <SEQ ID NO. 185> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 65:

*SHLFS FESLSLTHLE VCCSAFISTK TSIIIMRYLT VHVTVSFWIY
PTSTNVFFDC TLSTYFQTHI LKSSGPRKAP PKKSYRTIFT V*A*SLVNPF
LITSFSLFLL FVVIQVYNLL IFLIPSFYKP LLSSSSLL*W NHRLDCLNFF
SYPVALICCH ICIGYHICQA NNSIQSTTFS DCYLLLEKKN LKPSIL*THL
NPYCPKLSGL CI*LSLL

The following DNA sequence Seq-2292 <SEQ ID NO. 66> was identified in *H. sapiens*:

ACCTTCCCTCCTTACAAGGCCATCTCAATTATTATATGGAAATTCCATTTTACAGAGGCC

BNSDOCID <WO__ 0166751A2_I

AATGGTAACTTTCCAGTATAAACATAACAGAAAGCCTTGGAGACAGTGTCAAACTGCTGA
CCTGCTGGGCCTTTCTTATTCGCTGGATGAATCTGGGACTTCAAACAATCACTGTGCCTG
AACTAACGAGGGGGCTGTAAACATGCCTGCAAGTTCTCCCAGCTCCCCTTTTGGGGCCTG
AAAATTTATCTCTTCGCAGTGAGCGGAAATATTTTCCTTAGCTGGGTCCCCTGTTTTATG
CCTTTGATTTACAGAAGCTTCTCAACAAATAAATACAAGTTGACTGTTAGGTCACAGCCT
TTTGGAGAGCTTTCCAAAAGCCTTCAAGAGTAAGGGAGATAAACTGGAACAATATTTGGA
AAATAATCCCAGTTGTTTTATCACTTTCCTGGGGGCTGAGACGCTGATTGGATCTTGGCC
CCTCACCGGCACCCTATGAGGCAGACAGGGCTTCATTAGCTGCTTTCTGCATATAGAGAG
CGGAGACT

The following amino acid sequence <SEQ ID NO. 186> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 66:

TFPPYKAISI IIWKFHFTEA NGNFPV*T*Q KALETVSNC* PAGPFLFAG
IWDFKQSLCL N*RGGCKHAC KFSQLPFWGL KIYLFAVSGN IFLSWVPCFM
PLIYRSFSTN KYKLTVRSQP FGELSKSLQE *GR*TGTIFG K*SQLFYHFP
GG*DADWILA PHRHPMRQTG LH*LLSAYRE RR

The following DNA sequence Seq-2293 <SEQ ID NO. 67> was identified in *H. sapiens*:

CCCATCTAATAACAGAATATTGAAAAGGTCACAGCAGTACGGCTGAGTTCTCCAACCTAC
AAATCACAGGGAGCCGTCAGCCTCGGATAACTCATTCTCCTGACAAATCAAGGAGCAAGG
ACTGAAGACTGCACCGCTGATTAGGCTCATGGGAAACCAGAGGGCCAGGGAGAAATCGAT
AGAACATCCTGCCTCGTGCAGGGGTTCAGGGCAGCAGGGGTGCTGATTAGCAAATCAGCA
GGTGGGGGCATGCTGTCCCCTGGTGGCCGCTCAAATGACAGCCGCATTTGAAAGACCCCA
GAGGGGAGGTCCCATCTGGACCTGCCTGGGTGGTCCCCCTGGCTCAGCAACTTGGCTGGA
GATTGTTACCATTTTACCAGAAAACTATTAAAAAGCAGCTTTCCCCAAATAAAACATTTG
CCATTTAAAATCCCTAAAAGTTGATCTCTTTCAGGATATCTTGTGTTCTTTTTCCATTAA
GGGTTATTATTATTATTATTATTATTTTAGAAATTAACTTTTGCCATGACCAGCCTT
TTTGAGTTTTGACTGCAAGCAACAACAGTCAAAACTCAAACTCCTCGTAAAAGGAGGACA
GGTTTATGGCTTAATTTACTACAGAGTTCCACAAACAACATTAAAGAAAAATGACTGATT
TAATTAAAAACTG

The following amino acid sequence <SEQ ID NO. 187> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 67:

V FN*ISHFSLM LFVELCSKLS HKPVLLLRGV
*VLTVVACSQ NSKRLVMAKV NF*NNNNNNN NNP*WKKNTR YPERDQLLGI
LNGKCFIWGK LLFNSFLVKW *QSPAKLLSQ GDHPGRSRWD LPSGVFQMRL
SFERPPGDSM PPPADLLIST PAALNPCTRQ DVLSISPWPS GFP*A*SAVQ
SSVLAP*FVR RMSYPRLTAP CDL*VGELSR TAVTFSIFCY *M

The following DNA sequence Seq-2294 <SEQ ID NO. 68> was identified in *H. sapiens*:

CTTACAAGTGAATTGTGTGCATATGCAGGAGTCATCTGTAAACCTCACTTGATGTTTCCC
CTCTGAACTCTGATTGGTATACCTACAGCTATTATTTACTTCACCTCTACTCAGAGTTAT
CCAGAATGTTACGCATACAAAGGAGTATAAATAGGGAAAGCAGGTTATCAAACGCCGTGG
ATGGCATTTTCCCATTACACCTAGATACATATGAAAAAATGTACAAACGACTAGAATGAT

BNSDOCID <WO 0166751A2_I_>

TACACCATAGTGATAACAATGATTACTACTGGGTACTAAGATAATGTATTTTATAATTTT
TTCCTTTTGTTTATCTCTCTTTTCTGTTTTCTACATTGAAAATGTATTACTTGTTTTTAA
ATTAAAAACATTTAATTTGAATACCTATATTGAAGTGTGGCCTTACAGGCCTGGGTACCC
AGGAAGCCTGGTCTGGCCTGTATAATAATTAAGAAATAATTAATTGTATAATAATTGTGC
TTGTATAATAATTAAGAAATCTGCTACCTCCTTTCAGGTAGCAGCCCTTACCAGGGCTCT
AGAATCTCCTGAATCAGTTTAGTCTCCCTGAAGCCACTAAGATCTGGGCATGTCAAAATG
GGTGGACCCTGCCCAGTCAAAGCA

The following amino acid sequence <SEQ ID NO. 188> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 68:

CFDWAGST HFDMPRS*WL QGD*TDSGDS
RALVRAAT*K EVADFLIIIQ AQLLYN*LFL NYYTGQTRLP GYPGL*GHTS
I*VFKLNVFN LKTSNTFSM* KTEKRDKQKE KIIKYIILVP SSNHCYHYGV
IILVVCTFFH MYLGVMGKCH PRRLITCFPY LYSFVCVTFW ITLSRGEVNN
SCRYTNQSSE GKHQVRFTDD SCICTQFTCK

The following DNA sequence Seq-2295 <SEQ ID NO. 69> was identified in *H. sapiens*:

CGTTCAAAAATAAGCTATGTTTTGAAAATTAAACTATGCAATTGACACATACTGTATGGA
ACCAACACTTATTTTAAAGTGACAGAAAGAGTGGAATGTGGGAGAGCAAGCCTGTTTTCT
GATTGAACATACTAACAATTTAAAGGAAATCTTTGTCCTTCAGAAAAAGCACACAAGGAG
TATTACAAGGTGTTTGCCAGTCTTCAAACCAAGGCAAAGCAAGAACCACAGATGCCTCCT
CAAGAAATGCTCTAGGTGGCGAGTATCTTCTAAGGCTGTTACAAGTTCTTGATACAGCTA
TCTTTATAGGTGTATGATTATTATTGGAGATTAATACCTCAACTTTTTTAGAGTTCCAAT
GATTATAGATTAAAATTTCATAGTAATTCACATTGTTGTTCTGGGTG

The following amino acid sequence <SEQ ID NO. 189> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 69:

VQK*A MF*KLNYAID
TYCMEPTLIL K*QKEWNVGE QACFLIEHTN NLKEIFVLQK KHTRSITRCL
PVFKPRQSKN HRCLLKKCSR WRVSSKAVTS S*YSYLYRCM IIIGD*YLNF
FRVPMIID*N FIVIHIVVLG

The following DNA sequence Seq-2296 <SEQ ID NO. 70> was identified in *H. sapiens*:

ACTAGAACCCTCACTGATGGCTGGAGATGGCCGGGGCAGCTGTGCTGGGGCCATACGTTT
GGGATCTTGGTTCCCACTGTTGGCTGGGTTCCCTGGGTCTTCTGCATGTCATTTCTGCTG
CGATGGAATGTCCAAAAAGGTTCCTTTACTCACATGCCTGGCTGGGATAGACAGAGCAGC
CAGGGCTGGCCAGACACCTTTCTGTCTTCAGATGGCGTCTCCATGTGGGTACCTGGGCTT
CCTCACCACGTGAGTGATACTTGCTACATAGTGTCTGGCTTCTGCCAGAGCCAGCATTCT
AAGAGGCTCCAAGAGGCTTCTTACAACTCAGCCTCCCGTGTCCCAGAGTGTCACCTCTGT
CACATTCGCTGGATCACGCAAGTCACAGGCCGGCCGGTGTGCGAGAGGCTAGGAATTAGA
CTCCACTTTCCTTCAGGAGGAGAAGCCACCTTTAATTTACTACAAAAAGTTCCTTTTCAG
TGTTAACCTTAAAGTATTTTAATACGCTCAGTCAAAGTTCAACCTAATGTTCTATTTGAA
TATTTAATATGTTGTTCAAATGTTTAACCTAATAGCAGAGACTTTCATCGTAGCCCTTAG
AATCCTCGAACTATGAAAACATGCCTTTCAAAATTGATTGCGATG

BNSDOCID <WO 0166751A2_I_>

The following amino acid sequence <SEQ ID NO. 190> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 70:

TRTLTDGWRW PGQLCWGHTF GILVPTVGWV PWVFCMSFLL RWNVQKGSFT HMPGWDRQSS
QGWPDTFLSS DGVSMWVPGL PHHVSDTCYI VSGFCQSQHS KRLQEASYNS ASRVPECHLC
HIRWITQVTG RPVCERLGIR LHFPSGGEAT FNLLQKVPFQ C*P*SILIRS VKVQPNVLFE
YLICCSNV*P NSRDFHRSP NPRTMKTCLS KLIAM

The following DNA sequence Seq-2297 <SEQ ID NO. 71> was identified in *H. sapiens*:

AAACTCAGTGATTGTTTTAAATGCATCTCATCCCCATTAAGATATGAACTCTTTCCCCGC
GCCTTAACAAGTGAATTGTGTGCATATGCAGGAGTCATCTGTAAACCTCACTTGATGTTT
CCCCTCTGAACTCTGATTGGTATACCTACAGCTATTATTTACTTCACCTCTACTCAGAGT
TATCCAGAATGTTACGCATACAAAGGAGTATAAATAGGGAAAGCAGGTTATCAAACGCCG
TGGATGGCATTTTCCCATTACACCTAGATACATATGAAAAAATGTACAAACGACTAGAAT
GATTACACCATAGTGATAACAATGATTACTACTGGGTACTAAGATAATGTATTTTATAAT
TTTTTCCTTTTGTTTATCTCTCTTTTCTGTTTTCTACATTGAAAATGTATTACTTGTTTT
TAAATTAAAAACATTTAATTTGAATACCTATATTGAGTGTGGCCTTACAGGCCTGGGTAC
CCAGGAAGCCTGGTCTGGCCTGTATAATAATTAAG

The following amino acid sequence <SEQ ID NO. 191> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 71:

*LLYR PDQASWVPRP VRPHSI*VFK LNVFNLKTSN TFSM*KTEKR
DKQKEKIIKY IILVPSSNHC YHYGVIILVV CTFFHMYLGV MGKCHPRRLI
TCFPYLYSFV CVTFWITLSR GEVNNSCRYT NQSSEGKHQV RFTDDSCICT
QFTC*GAGKE FIS*WG*DAF KTITEF

The following DNA sequence Seq-2298 SEQ ID NO. 72> was identified in *H. sapiens*:

CTTTCCTGTGCTTGTCTCACCTGTCAATCTTTGTGAGCTTGGCTATGTGAGATGATCTGT
AGAGACTGATCACTTCTGGGTACACAAGCAATGAATTTCAGGCCTAGGAAATGAAGCACC
AGATGGAGATGTGATGCCCTCCCAAAAGTCTTGCCCCCTTTACACCCTTTCCCTGGGTGA
CTTTTCTCAGTTGGAATTGCTTGCCTCCTTCAAACTGACAACAGATTCAAGGGTTCCTGC
AGGAAAATCTCCCAAGTTTGATGCTGTTAGATAATACATCAGCGGTCAGGGAGTCCTCAT
CAAGTTGAGTCCAGCACTGGCATGGTGTGGAGAAATGGGGATGGGTGGCACAGAGGAAAG
AGGGGACATCTCCCTGCCCTCCGGGAGCTCCAGCAGGGAAGGCATTGCTCCTGGCAGACC
AGGAGTCACATGTCAGCCTCTTGGGAGGAGATGGGGGTGGGAGGGAGAGGATAATAA

The following amino acid sequence <SEQ ID NO. 192> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 72:

IILSLPPP
SPPKRLTCDS WSARSNAFPA GAPGGQGDVP SFLCATHPHF STPCQCWTQL
DEDSLTADVL SNSIKLGRFS CRNP*ICCQF EGGKQFQLRK VTQGKGVKGA
RLLGGHHISI WCFIS*A*NS LLVYPEVISL YRSSHIAKLT KIDR*DKHRK

BNSDOCID <WO_ 016675 1A2_L>

The following DNA sequence Seq-2299 <SEQ ID NO. 73> was identified in *H. sapiens*:

GAAAGTAGCTAATTTATGTAAACGCCACGAAATTAGAAATTAAATAATTAAAAAAATGAT
ATTCTGAATTGCTAAGGCTCCAGCCTCCACCACTGTGATTTCTTTGTATCAGTTTGCTCA
AAGATCCCACCATATTTTCTCAGGAACACATCCATTATACTTCTGTGCCAGTCTCTTCAT
CATATCACAATCACATCGTAGTTCTAAGGTCAATCTCCCTGACAAAATTGTTTTTCTGTT
GGTCTTATCTAATTTTCTGGTTATCTATGACTATGTAACAAAGTATCTGAAATTTAGTTG
CCTTAACAAACAAACATTTTATTTTATCACCTGGTTTTGTGAGCATCACTTACAGCTTAG
TTTGTCAATTTATGTGATTTGTGAGGCATTGACTGGGGTCACCGTGTGTTATTCAGCTTC
GTGTCTAAGACTGTCTAGAGAATAAACAATCATTTCTTTGCCTGCCATCGCGG

The following amino acid sequence <SEQ ID NO. 193> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 73:

KVA NLCKRHEIRN *IIKKMIF*I AKAPASTTVI SLYQFAQRSH
HIFSGTHPLY FCASLFIISQ SHRSSKVNLP DKIVFLLVLS NFLVIYDYVT
KYLKFSCLNK QTFYFITWFC EHHLQLSLSI YLICEALTGV TVCY$ASCLR
LSRE*TIISL PAIA

The following DNA sequence Seq-2300 <SEQ ID NO. 74> was identified in *H. sapiens*:

TAATATTCACTGAAATATTCAAAGTCAATTTGGACAGAAGTTTGTATCCGTTTAAATGTT
TTTCTGTAAAACTATATTTAATTCAAATCTTATATCCAGTTGATTGCAGATTAATTTACT
TCAACGAGCATTTATTAAATCGTACTATGCATGAGTATATTTCTGAAGGTCATGGCCTTA
CCTTGGAGTATGTGGCCTTTCCATTTTCTTACTGAAATATCTGTAGGTTGAGATAATAGT
GACTTTCTATAATTGACTTACTGAAATTCTCTATTTTCAATGCTATCAATGATTTAGATA
TGGTTTAAAAACTCGTGTTTATTCACTTTTCAGCTAAAATATAAAGTGATGGCTCAGTGG
TTTCTTGATGAGGAAATCAAGAACTGTAGCACATTTTCTATTACTAATTTTATAGAATGA
TCTTTAGTTAAATAAAAAACTTACAGTTAATATAAATAGCACTTAGAAGAATAGCATTTC
ATTTTGAAACGAAGTCTCAAGTCATGGATTTTCATTTTCTAGGTCTGTAATATAGCAATA
TGCATTGCCTTCTGAGTG

The following amino acid sequence <SEQ ID NO. 194> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 74:

IFTEIFKVN LDRSLYPFKC FSVKLYLIQI
LYPVDCRLIY FNEHLLNRTM HEYISEGHGL TLEYVAFPFS Y*NICRLR
*LSIIDLLKF SIFNAINDLD MV*KLVFIHF SAKI*SDGSV VS**GNQEL
HIFYY*FYRM IFS*IKNLQL I*IALRRIAF HFETKSQVMD FHFLGL*YSN
MHCLLS

The following DNA sequence Seq-2301 <SEQ ID NO. 75> was identified in *H. sapiens*:

AACTCACAGCTAAACAGCCTCCCACTGTGTTTCCCGCTAATGGCCCTTGTGGGCCCCACT
ACAAATCCCCACAGGCGGCTTAGCCTCTTGATTGTTTCTTTCCCTGCCATCTCCTGTGGC
CTTGGGGGAAGACTCTCCCTTTCCTCACCACAAATGCTGTTCCCCAATTTGTAAAACAAG

ENSDOCID <WO 0166751A2 I >

TTTTCTGGTTGGAGAACAATTGCTAGGCTCCTTGGTGCTGTAGCATTCCTTCCATTCAAT
CCATTGGCCCCTACAGG

The following amino acid sequence <SEQ ID NO. 195> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 75:

PVGAN GLNGRNATAP RSLAIVLQPE NLFYKLGNSI CGEERESLPP
RPQEMAGKET IKRLSRLWGF VVGPTRAISG KHSARLFTSQ

The following DNA sequence Seq-2302 <SEQ ID NO. 76> was identified in *H. sapiens*:

GCAAGTTTTTTTGCTTTCTTTTTTGATGGTGGCACTTTATGAATTGTTTTCTCTTTTTAG
AAATTAAAAAATAACACTAGGTACATTATTTAAATGTCTCTGTGATGATTGATTAAACTT
TTAGACAGCATTTATTTACTCCCAACTATAAAAAGGAGAGTGTGAAGACACTTATAGTTC
CTACTATAACCAAAAAATACACTTAATCATCCTAATAATTATTTTTCTTATAACACAGGC
CTGTACTATTACCTCATATTATGTGATGATAAGCTCCACAGTTGTTTGGCCCTGTTTCTA
TTTCTCAGTGGTCTCAGGGTTCATTGCCATTCCCCAACTCCTTTTCAGCTTTCAGCGATT
TAGTTCCATTTTTTGTTTGGCTGTATTTTATCTTATCTTCAAGGATTTTCTTTTCAAGAG
ATTTCATGGTCATTATATTCTTCAAGCCTTTACAAGTGGAATAGATCTGTTGCGGTCATC
TATCAACAACAAAGTAACAACTCGGCCATGTAATCCCTGGGTCACACTACCTTTTCCCCT
TCTGGGCCCATAGGTACTGCTCTACTGTCTTCTGGCAGTGATTGC

The following amino acid sequence <SEQ ID NO. 196> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 76:

ASFFAFFFDG GTL*IVFSF* KLKNNTRYII *MSL**LIKL LDSIYLLPTI
KRRV*RHL*F LL*PKNTLNH PNNYFSYNTG LYYYLILCDD KLHSCLALFL
FLSGLRVHCH SPTPFQLSAI *FHFLFGCIL SYLQGFSFQE ISWSLYSSSL
YKWNRSVAVI YQQQSNNSAM *SLGHTTFSP SGPIGTALLS SGSDC

The following DNA sequence Seq-2303 <SEQ ID NO. 77> was identified in *H. sapiens*:

GTTTTTGAAGATGGAGGTGGCACAGCAGCAGCGATGCATCTGAAATCAAGGTGCACTGAG
GACTGTGGCAGCCCTAGCAGAGAGGAGAGAGGCAGGGAACAGATTCGCCCACAGAGTTTG
CAGAAGGAATTCACCTGCCGACACCTTGATTTTGTGCTTCTGGCCTCCAGAACAATGAGC
CAATAAAGGTCTATTGCTTTATGCAACCAGGTTTTGGTAATTTGTTACAACAGCCCTAGG
AAACTGATCCAAAGTCTTTAATTAACACAGTATCTATAACTGGTGTTCTGGCTATCTCTA
CCCTTATGGAAATTTTAAGTGAATGTAATATTTCCTTCCTCATATTTTGCTATTTGTTCA
CATATCTGAAGCATGGGTTTCTTTTCAGTGGGTAGATTTTCATTGGCCAAAGGGTACCTC
TGTGCTCTGTAGTCTGTTTGCGACACCTTAAACCACAAGGGCTCCCTCACAGTGCTTCCG
CCTTAGGTCAAACTCCCAGAGGCAGACCCTGAGGCAGGGATTTGGGCAAATGTGGCTGAG
ACTGAGGGAATGCACTTCAGGAGCACAGCAACAGGGCT

The following amino acid sequence <SEQ ID NO. 197> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 77:

SPVA VLLKCIPSVS ATFAQIPASG
SASGSLT*GG STVREPLWFK VSQTDYRAQR YPLANENLPT EKKPMLQICE

BNSDOCID <WO 0166751A2_I >

QIAKYEEGNI TFT*NFHKGR DSQNTSYRYC VN*RLWISFL GLL*QITKTW
LHKAIDLYWL IVLEARSTKS RCRQVNSFCK LCGRICSLPL SSLLGLPQSS
VHLDFRCIAA AVPPPSSK

The following DNA sequence Seq-2304 <SEQ ID NO. 78> was identified in *H. sapiens*:

AAATCTATCTCCAGAAGTGGAATTGCTCCCACAGAGTATATGCTATTTGAAAGCCTGCTT
TATAGCTTGTCTGAGGGTGATGGAGCCCACCCCGTTCCCCAGAGGGAAACAGCCACCAGC
TCCAGCCTTGGCATGGGAAATGATTTTCTCTGGGGCCTCCATGGAACAGACAGCTCTTCT
CACATTCCCTCAGAGCAGAATAGTTGTCCAAGAAATGTAAAAACATTCAGGAACATTTGA
GACACTTCTCTTTGGTTTTTGGTTGTGCTTTGGGGCTAACATTGGCCTGGAAGGTTGTCT
AATATTTGGAACGTCTGATGTTTTGGCTGACTCAGGGCCAATGAAACAAAGCTGTGTTGG
TGATTTCAAGGCGGCAGCTGCCTCCTCCTTCCCCACTCACCATGGTGCTTGGGGTGAACA
GTTTTCCAGCCCAGGTTCAGACTGGTGTAAATACTCAGCCCCTGTGAAATTGACTTGTCT
ACTGCTCTCTCTCTCTCTCTCTTTCTCTCTCAAAGAAGGAAAGAAAGAAAGACGTTGAAT
TGTGTGTTGATTTCTAAAAAATCTTCTCTTCCATTTTCTCCTGGACTTTCCATGAGCAGG
TAGTGCCCACCTGAATGCCAGCTGAGCCGGAGGTGTCAAACAAGATGCAATACAGTCAGG
CCAGAAATAGACTTTCCCGTCACGTCTACTCTGCG

The following amino acid sequence <SEQ ID NO. 198> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 78:

QSRRD GKVYFWPDCI ASCLTPPAQL AFRWALPAHG KSRRKWKRRF
FRNQHTIQRL SFFPSLREKE RERESSRQVN FTGAEYLHQS EPGLENCSPQ
APW*VGKEEA AAALKSPTQL CFIGPESAKT SDVPNIRQPS RPMLAPKHNQ
KPKRSVSNVP ECFYISWTTI LL*GNVRRAV CSMEAPEKII SHAKAGAGGC
FPLGNGVGSI TLRQAIKQAF K*HILCGSNS TSGDRF

The following DNA sequence Seq-2305 <SEQ ID NO. 79> was identified in *H. sapiens*:

AATTCTGTTACTAATTAAGACACTAAGTTGTTCCCGAACTGTGAAGCTTTTGAGTGTTCA
AATGTATAGGACACATTTATATGAATTGTTGTTTCTATAAGATTTCCAATTTCATCCCAC
AAATACTCTCTAAAAGCTATTACATTTTATTGCATTATTTATTAAGCAATTGAGCTCAAT
CTTTTTATGCCACATTTTATATTCTAAAGACATGTTATATTGTCTTAAACATACTTGATC
CATTTTGTATGCACAGTTTATTATATTTATAGATGTGACATTTACATATCTGATCAAGCA
CAAACCATCAGCACACAATGCAATATGATACCTTAGTTTAATTCAATTTCACTTTCGACT
GGTTCCATCTTTAAATATTAATTTAGGTAAATGTGAATGCACAATAGTGTAATTACTTCA
GAGCAAAAACACATTTTGTCTATTTTTAGAACTATAGAAGTAAAATGTGTGTTTACTTTC
CAACTATAAAAAACGTACTGAAAGGTGTCATGCCCTCAGCACTCCAAGTGGCTTCACTAA
GAAAACA

The following amino acid sequence <SEQ ID NO. 199> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 79:

F S**SHLEC*G HDTFQYVFYS WKVNTHFTSI VLKIDKMCFC
SEVITLLCIH IYLN*YLKME PVESEIELN* GILHCVLMV CA*SDM*MSH
L*I**TVHTK WIKYV*DNIT CL*NIKCGIK RLSSIA**IM Q*NVIAFREY
LWDEIGNLIE TTIHINVSYT FEHSKASQFG NNLVS*LVTE

BNSDOCID <WO 0166751A2>

The following DNA sequence Seq-2306 <SEQ ID NO. 80> was identified in *H. sapiens*:

AGAAATGTCCTTTTGAGCCCCAAGGCGTGAGGGGAGCCTCTCCTGCATGTGAAATGCCTA
GTACACCCCACCGTCCTTGGATTGTTTCTAACCCCAAGTTTTCTCTCCACATTGTCAGAA
GTTCAGTCAATTGGAGATACAGTTAGGTTAACAAGTACCCTTTTAAAAATGTCTCCCCCC
AATTCATTCTTCAAAGTACAGGTGGGGCTTGATGTAGAGCAGCATAAGGACCCCAGAACC
CTGGAGGGAGAGTCACTAGGAGGTTGGAGAGGGGAAGATGCAAAAGATAAACTTCCAAGA
GATCAGCACTTCACTCAGGGCCAACCTTTTCCCCAGG

The following amino acid sequence <SEQ ID NO. 200> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 80:

PGEKV GPE*SADLLE
VYLLHLPLSN LLVTLPPGFW GPYAALHQAP PVL*RMNWGE TFLKGYLLT
LYLQLTELLT MWRENLGLET IQGRWGVLGI SHAGEAPLTP WGSKGHF

The following DNA sequence Seq-2307 <SEQ ID NO. 81> was identified in *H. sapiens*:

AGTGTAGAATAATAGACATTGGAGGCTAGAAAGGATGGAGGGTGGGAAGGAGGTAAGGGA
TTTGAGGGATGAGAATTTACTTAATGGGTGCAATGTACATTATTCAGGTAATGGTTACAA
TAGAGGCACAGACTTCGCCACTCTGCATTGTATCGATGTAAAAAAACTGCATGTGTACCC
CTTAAATTGATACAAATAGAAAAACCCCATATAGTATTTGAGGTGAATAGATCTAGATGG
TCCCTCTTTAGTGAGTGAATCCTATAGAGAAGTAATAAACACACACATAACTCTGGCACA
GTAAATAAGCAAACATGAAAATGGAAAAGCATCAAAGCAGAGTGATCTATCTCAAGATCC
TGACTGACTTGATGTACAAGTTGGACAAGTTTCAAAACTAGTATTTCTTTCATGTCTCGG
CAACATTTCAGAAGAAGGTGCACCTTGACGCTAGCCATATCAGTAGAAGATTTCTTTCCT
CAAAGAGATTGCCTCAAGTCCTCACCCAATGTGATGCTAATGACTTAACATCAGGTTCAC
CTGACTTAAACATATTTTTACTTATTATTATTATTATGATAACACTGGACCTCAACATAT
AGTTTCCTTTGTTCCACATTTCAAAGAGAGATATCAA

The following amino acid sequence <SEQ ID NO. 201> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 81:

D ISL*NVEQRK LYVEVQCYHN NNNK*KYV*V R*T*C*VISI
TLGEDLRQSL *GKKSSTDMA SVKVHLLLKC CRDMKEILVL KLVQLVHQVS
QDLEIDHSAL MLFHFHVCLF TVPELCVCLL LLYRIHSLKR DHLDLFTSNT
IWGFSICINL RGTHAVFLHR YNAEWRSLCL YCNHYLNNVH CTH*VNSHPS
NPLPPSHPPS FLASNVYYST

The following DNA sequence Seq-2308 SEQ ID NO. 82> was identified in *H. sapiens*:

AATTTGGAGAGGGCACAGAAGAGACAGAGAAGAGATGACTTTTTTCTGTTTCATGATGTC
TGGGACCCCAACTGGGAAGACACAATGAGCAGAACTGCTGAGTGGAGTGTGTGCACATGA
CTCCCCACAGAGCCAGGCTTCCTCACAGCATGGCAGCCTCAGGCTCCAAATGCGTGTATC
CCAGCAAATAAGGCGAAAGCCACATCACTTCTTATGACTCAGCCTCATAAAACACTAGGA

BNSDOCID <WO 0166751A2_I_>

TCACTTTTGCAATACTCTATTGCGTGAAGCAGCCTCAAGCCCACCCAGGTGCAAGGGGAA
GGGGCATAGAATCTAACTTTCAATGGGATGACTGTAAAATAAGTTTGTGGCCATTTAAAA
AACTGCTATGAAAAGACAGTGCCTTAGTAATTTGGGGAATCGGGAAGTCTTCACTGAAGA
GGTGATGTTTGGGATGCATCTTGAAAGAGGGACAAAAGTTTGCCAGGAGAAGTGGGGTGA
AAAGAGAAATGATTCTTCATAGGGAATGGCACCTTTTAGGCTTACATGTACACAGGAAAT
ACTGAAATACAAGAAGGAGTACAAGGGGA

The following amino acid sequence <SEQ ID NO. 202> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 82:

PLVL LLVFQYFLCT CKPKRCHSL* RIISLFTPLL LANFCPSFKM
HPKHHLFSED FPIPQITKAL SFHSSFLNGH KLILQSSH*K LDSMPLPLAP
GWA*GCFTQ* SIAKVILVFY EAES*EVMWL SPYLLGYTHL EPEAAML*GS
LALWGVMCTH STQQFCSLCL PSWGPRHHET EKSHLFSVSS VPSPN

The following DNA sequence Seq-2309 <SEQ ID NO. 83> was identified in *H. sapiens*:

AGTTTCTCATCTATTAAATGGGGTTAATCATGTCTATTTGTATCTATTTCCAAAGAGTGT
TGTGAAGATCCAAGGGGATAGCACGGTGTAAAGCACATTCTTCTTACCTTTTATCTCCCT
GAGCTGAGTGTAGAGGCTGCAGTCATTCATTGAACAATTGTTTATTGTCTACTTATTGCT
AACCATTGTTGCGGGTTCTGCGGAAACAGTAATGAACAAAAGTCTCTGTTCTCATCAAGT
TCACATTCTGGTGGGGAAGCTTGAAAATAAGTAAGTAAACTAAGCAGGATAACTTCAGAT
AGTGATAAAAGCTATACAGAAAAGGAAACAGGCCCATAGGATAGAAGTGATTTGGTGGGA
GGCCTGAAGAGGCTTTAGGGAGCACAGTGGTCTTTGAACCAAGACCTGGAGGCCAAGAAG
GAGCTGGGCCTGCGGAGACCTGAGGAAGAGCATTCCAGGCAGAGAGAAGAGCAA

The following amino acid sequence <SEQ ID NO. 203> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 83:

LLFSLPGM LFLRSPQAQL LLGLQVLVQR
PLCSLKPLQA SHQITSILWA CFLFCIAFIT I*SYPA*FTY LFSSFPTRM
T**EQRLLFI TVSAEPATMV SNK*TINNCS MNDCSLYTQL REIKGKKNVL
YTVLSPWIFT TLFGNRYK*T *LTPFNR*ET

The following DNA sequence Seq-2310 <SEQ ID NO. 84> was identified in *H. sapiens*:

CATCAAAGATGTAGACAAAATCAGATTACTTTTAACCTTCTGAGCCACAGTAAGGACTTG
TAACTTATGCTATTCCACTTATAATGGAAAGTCATTAGATACTTTTTATTATAGAGATTT
ACATGGTCTGTTGTTGTACCTTATAGAAAAAAAACATCATTCTGGCATCTGTGTGGAGAC
TGGACCATGGAGAGTGAGAGGAGGAAACTGGGGGATAAGGGAGGAAGACATAGCTGAAGT
CTTCATAGCAGAAGATGGTGGCTTATATTAAGGTAAAAGAAGTCGAAATTGTGAGAAGGG
GCCAGATTTGGTATAGTCTGAAGTTAATGTAGTAAATGTGGGTAGTGAGGGAAGAAAGAA
TGGTCACAATGACTCCTACATCTTAGCCTTTGTAAGTAGGTGAATGTCAGGTGCTTAAGT
AAGATGGAGGACTTTGAGGGTGTAAGCAATGGGAGTAAC

The following amino acid sequence <SEQ ID NO 204> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 84:

ENSDOCID <WO 0166751A2_I_>

IKDVDKI RLLLTF*ATV RTCNLCYSTY NGKSLDTFYY RDLHGLLLYL
IEKKHHSGIC VETGPWRVRG GNWGIREEDI AEVFIAEDGG LY*GKRSRNC
EKGPDLV*SE VNVVVNVGSEG RKNGHNDSYI LAFVSR*MSG A*VRWRTLRV
*AMGV

The following DNA sequence Seq-2311 <SEQ ID NO. 85> was identified in *H. sapiens*:

TTGGAGACTCCTCCCTTTCGAGGGCATATCTTTTACATTCTAGGCTCTCTACAATTATCT
ATTTCTCTAATTGCCTCTTTCACTTGTGTTTTCTCCAATTTCTGATTCCCTTTGCAGCTT
GTCTGGATTTAGACTATGCATGAGCAGGAACAATAGATTCACCCCATCTGCTGGGATTCA
GGCACTTCACTTTTTTTGTTGTACCTTCTGGGAACCTTACTATCTTTTGCATCTCACCCA
GATTCCTGAAATCTTGTTGAATGCATTTGTAAAAATTATTTTTCTGCTAACCGTGACTAT
TACAAGCCTACGTTATCAGGACAATAAGAGTAGTATGCTACCCTTGACACCTGCTCCTGT
CTCAGCTCAGAAACCACAGAGGACATGGCCACAAGCAAAATATCAAACTGACTGAAACTA
TTCATATTTTTCCTGTAAGTCTTAACCTTTTAGTTAAATTACCACAAGTATTTTAAAATT
TTTATATTAAAAATCAAAGATCAGTCTGAAAATAATAACATTTTTCTTTTAATTTCTCAT

The following amino acid sequence <SEQ ID NO. 205> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 85:

WRLLPFEGIS FTF*ALYNYL
FL*LPLSLVF SPISDSLCSL SGFRLCMSRN NRFTPSAGIQ ALHFFCCTFW
EPYYLLHLTQ IPEILLNAFV KIIFLLTVTI TSLRYQDNKS SMLPLTPAPV
SAQKPQRTWP QAKYQTD*NY SYFSCKS*PF S*ITTSILKF LY*KSKISLK
IITFFF*FL

The following DNA sequence Seq-2312 <SEQ ID NO. 86> was identified in *H. sapiens*:

ATTAGAGGATGATAGACCTCCTGCTTTTGTCATGAACAGAAATTTGTTGGTTTATGGAGA
GAAGGATGAGAAGGACTTACCCTCCACTCACCTGACTCCAAGAAGGCAAATATCTGGAGA
AACCAGAGACAGAAACCCCCAAAGATCTAAACTCTCTGTAGAGAGCATGCAGTGACAGTT
TAGCCTATGCTACCTGAAGTGGAAATAGATCATTCTTTAAATAAATCACTTGTGCTGACT
TGGTAACTCAAGGAGACCACACTTATTATTTCCTCTCAATTCGCAACTATCTTTGGAAAC
AAGACGATTTTATTTCTTGCTTAGCCTTACCTCTTCTATTCACAGAAAATCAGCAGCACG
CTAATGATGTCTTAAAAGTACAAAGTCACTTGTAAAGGACATTAGGATCCCTGGCTAGGT
AAGAAACTCTGTATGACACAGTTTTCAAGTGCACACCTATTCAAAATTGCAAGTGATATC
TCTTTTGTACTGATTTAGCCTGTACCTGAAAGCAATAGCCATACACATGAGTATACTGAA
TTAAGTGCACTAGTAGATGACTCTCTATAAGAAAGAGGGGGAAACACCCAAATTACATTC
AAAGACATTACTGGAAATTAATTATGTTAATTCCCAGTATAATGCAACATTTA

The following amino acid sequence <SEQ ID NO. 206> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 86:

*RMIDL LLLS*TEICW
FMERRMRRTY PPLT*LQEGK YLEKPETETP KDLNSL*RAC SDSLAYAT*S
GNRSFFK*IT CADLVTQGDH TYYFLSIRNY LWKQDDFISC LALPLLFTEN
QQHANDVLKV QSHL*RTLGS LAR*ETLYDT VFKCTPIQNC K*YLFCTDLA
CT*KQ*PYT* VY*IKCTSR* LSIRKRGKHP NYIQRHYWKL IMLIPSIMQHL

BNSDOCID <WO 0166751A2_I_>

The following DNA sequence Seq-2313 <SEQ ID NO. 87> was identified in *H. sapiens*:

AACAGTATTTCTGTGCTTAGGTAAATTAACATTGTTTTGTTTCTTCTGCATATTTAAAAT
AATTAAATCTTTAGGACCTTCTATTAATGGCCCCATAGAACAATACAAGCATAGCTATAA
TTTCCAAAATAGAAATAAATATTCATACATGGTCTATGAGTGTCCTCACATGTAATATAT
GGCTAACTCAGACAATGATATGTTGCACATTCTATAATGATTAACAGCATTGCTTGCACA
ATTACAAACAAATGTTGAGATTTTATAAATACACATGCACACATGTATAATCCATATATA
CATGTATGTTTAATATATATTGATAGTTTTGTTATGCTTCAATTTGTATCGTGTGGTATT
ATTCACCTCACAACCGCTAGTAGTTATAAATGAAAAAAGTTTATGCAAAACTGTATTTCA
GTTTTTTAAAAATATCATTCATTATCTAGCTATTTTGTGGCCAAATTTTGTTCATTCATG
TCTTCATTCATTCAGTAATTATTAGAACCTGTTCTAGGCATTAGGCATTTAAAGAGAAAT
ATGATGCATTCCATATCTTCTGGGAGATCATAGTCTCCTGGGAAAGATAAATAT

The following amino acid sequence <SEQ ID NO. 207> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 87:

QYFCA
*VN*HCFVSS AYLK*LNL*D LLLMAP*NNT SIAIISKIEI NIHTWSMSVL
TCNIWLTQTM ICCTFYND*Q HCLHNYKQML RFYKYTCTHV *SIYTCMFNI
Y**FCYASIC IVWYYSPHNR **L*MKKVYA KLYFSFLKIS FII*LFCGQI
LFIHVFIHSV IIRTCSRH*A FKEKYDAFHI FWEIIVSWER *I

The following DNA sequence Seq-2314 <SEQ ID NO. 88> was identified in *H. sapiens*:

CAGGACAGAAATAGTTATACAAACTGTTAAATGAAATCCTAGCATGAGAAATACAACAAA
GTATGTACAAAAACATCTGTACATTTATATTTGCAAATGCATATACAAAAGGATAAGTAG
GCTACAAAGTTATACTTACTTAGAATTAGTATTTCATCTTGAAACTAGCTCCCAATATAA
CTACAGCATAAGGAGACATTTTATTAGAAATTTAAATTTCAAGGTAAGAAATTATCTCAT
TGAAAATTGTGATATTATTTTACTCAAATTACGTATAGAAACTCATACAATTATAATTAC
AAAAGTTCCAACTTCCAGTTACCGAAATTTACTATGAGCTCAACAAAACATCACCAAAAA
GTATCCATACATTAAAAAAAAAACCTATTTCATACAGAATTATACTGTTTTAGCCAATTA
AAAAAAAAACGCCTTTTATTAAAGGCAAACTAGAATTTGGCAACTTAAGTCATTATGAAT
AAATACATGTGTTCAATTCAACAAGTTCCTACATCCATTCGCCTTGCACT

The following amino acid sequence <SEQ ID NO. 208> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 88:

VQGEWM *ELVELNTCI YS**LKLPNS SLPLIKGVFF LIG*NSIILY
EIGFFFNVWI LFGDVLLSS* *ISVTGSWNF CNYNCMSFYT *FE*NNITIF
NEIISYLEI* ISNKMSPYAV VILGASFKMK Y*F*VSITL* PTYPFVYAFA
NINVQMFLYI LCCISHARIS FNSLYNYFCP

The following DNA sequence Seq-2315 <SEQ ID NO. 89> was identified in *H. sapiens*:

TTTTAGTTCTTAAGAACACAGGCTAAGGGAGAAGAAGGAGGAATTGAGGGTGGAAGGTTG

ENSDOCID <WO__0166751A2_I_>

CCCATAGTGAAGCCCAGAGAAAAGAGAGAGTAGAGACATGAAGGGAAGGGGCTTGGGGGT
TCTTACCCTCCAGAAAGCCGGGAAAGGGGTCAGGGCACAGAGATATGAGGTCGGGGCGCA
GAAATAAGGGATTGGGGTGCAGAGATATAAGAGGTTGGGGCATGGAAATTAGGGATCGGG
GCGCAGAGATATAAGGGGTTGGGGTACTTGCCCCTCCCCCAGAAAAGTGGTACTTGCCCG
CTAAGGGTGAAGGAGAAAGGGGTTGGGGGTTTCTTGCACCCCAGAAA

The following amino acid sequence <SEQ ID NO. 209> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 89:

FLGCK
KPPTPFSFTL SGQVPLFWGR GKYPNPLYLC APIPNFHAPT SYISAPQSLI
SAPRPHISVP *PLSRLSGG* EPPSPFPSCL YSLFSLGFTM GNLPPSIPPS
SPLACVLKN* FWGARNPQPL

The following DNA sequence Seq-2316 <SEQ ID NO. 90> was identified in *H. sapiens*:

ACAATTCTTCCTAACAGGATTGTACATGTATATTGTATTGTCCACATTCATACTACATAT
TTTATTTCTGTGTCATTGCTAGTTTTGAAGGATTTATAATTGACAGATGGTACCAAATGC
AGCTTTCTCCCCTTTGCCTATTGTGAAGAGGAGACCTTTGCCAAAATTTCACAATATGAA
AATTGCTCCTGTTTCCTAAAGGGCAAAAATGAATCACTTTCTTTTTGGATTAGAAACAAG
TTCAGGATGGCACAGAAATACATTGACATGAACTACTTGCCGGAGTGCTGACATCCAATG
CTGTATATATTTTTGGGAGAAGATTTCTGGCTTTTCACCATAGAATCACTGGTTACCAAT
GTGTTAAAATTGGAGTCAAGGCACTTTAGGTCTTCTTACATGGAGTTAAGAAAATTTAAA
GCAATTTTGTAAATGAAGAATTTCACAATGCATGTCTATTATTGCTCTTTCATTCCCAAT
CTAATCATTGTTAAAGTGTTCTAAGTTTCTTCTACAGTAGTCG

The following amino acid sequence <SEQ ID NO. 210> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 90:

TILPNRIVHV YCIVHIHTTY FISVSLLVLK DL*LTDGTKC SFLPFAYCEE
ETFAKISQYE NCSCFLKGKN ESLSFWIRNK PRMAQKYIDM NYLPEC*HPM
LYIFLGEDFW LFTIESLVTN VLKLESRHFR SSYMELRKFK AIL*MKNFTM
HVYYCSFIPN LIIVKVF*VS STVV

The following DNA sequence Seq-2317 <SEQ ID NO. 91> was identified in *H. sapiens*:

CTGGCAAGGAGTGTTTTAGCCTAGCCCAAAAAGACACCATTTTGAAAACTATATATAAGT
AATGTGGTAATTAAAAACCAGTCAACTCTCTATTATTGGGGCCGCAAAATACTTCTGTAA
TACTTTGGCCAACATGAATTGGTTACATGTGCCTTAAAATTTTTTAAATTATATTTCTAG
GAAAAATCAATCATCACTTACAAATTGTTTTACAATCTAAGAACTATACATTTCTCTAAG
TAAAATTATAAATCCCAGGCATGTAACTATTCACATCAAATTTTGTTTTTCAGACAAAGG
CATTATCCATCACAATAAGTAACTTTTTGTCTTTATTTCAACCGGACAATCGTGATTAGA
AAAGGTAAGAAGCCATCTATACTTTCCCGTTCCATCCAATACATTTTTGTTACTATTTTA
TTTAATTCAATGTTTTTCTTTTTTAAAAACTATTCAGCTTAAATACTGTACCAAAAATAA
TTTTAATATTAAATATCTGCAATTCTATTCTAGCTCCTGTGACAAAATTCAAGAAAACCT
GACATAAATGAACAACAATACAACATGTATTCAACCATCTATGATCTCTTCCATGGCTTT
ACCAATCATTTACATCCTCCTTTGTATTGGTGGTGTTTTTGGAAACACTCTCTCTCAATG
GATATTTTTAACAAAAATAGGTAAAAAAACATCAACGCACATCTACCTGTCACA

BNSDOCID <WO 0166751A2 I

The following amino acid sequence <SEQ ID NO. 211> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 91:

WQ GVF*PSPKRH
HPENYI*VMW *LKTSQLSII GAAKYFCNTL ANMNWLHVP* NFLNYISRKN
QSSLTNCFTI *ELYISLSKI INPRHVTIHI KFCFSDKGII HHNK*LFVFI
STGQS*LEKV RSHLYFPVPS NTFLLLFYLI QCFSFLKTIQ LKYCTKNNFN
IKYLQFYSSS CDKIQENLT* MNNNTTCIQP SMISSMALPI IYILLCIGGV
FGNTLSOWIF LTKIGKKTST HIYLS

The following DNA sequence Seq-2318 SEQ ID NO. 92> was identified in *H. sapiens*:

AACATGACATAGGAAAAGCTAGACAGTTGGTCTCAGCAAAGTGGCACTCCCACTGAAACT
GAATATTAACCTGCACCTAGTATTTTGATCAGTACACTGATCTCTAATTAAGACAAGGGC
TCTCTGTGACAGTTCCATTACCTCAAATCTAAAATAAGGTCACTCCTGTACAGTGCTGTC
TACTTTCCTTTTCTGCATAGAGTTATTAGGCTCAAATAAAATAAAATAAAAACTATGAAT
AGTTGTAATATACTCTGTAGATGAGAGGAATTATTTTTTATTAAATACTAAAAATTCCAG
TACCTCATGTGCGACTACAAACCTGTGACTACCTAAAGCATGAAAAGCAGACACAGGTGC
ATAGATCGGCATACAAAAGTAATAGTACTGAAGATACCACATCTCTATCCTCATCTGAAA
CAGAAGGAAATCAAATGTGCACCAAGGCTTACTGAATTGCTACAATGTTGGAGA

The following amino acid sequence <SEQ ID NO. 212> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 92:

SPTL*QFS KPWCTFDFLL FQMRIEMWYL
QYYYFCMPIY APVSAFHALG SHRFVVAHEV LEFLVFNKK* FLSSTEYITT
IHSFYFILFE PNNSMQKRKV DSTVQE*PYF RFEVMELSQR ALVLIRDQCT
DQNTRCRLIF SFSGSATLLR PTV*LFLCHV

The following DNA sequence Seq-2319 <SEQ ID NO. 93> was identified in *H. sapiens*:

TTGTCTGTAAATGGCGTTAGTTTCCCTAATATCTACAAGTTATTAGGAAAATTAAATGAT
ATGCTAATCTAAAAACTTGCCATTCAATGAATGTTAATTAATTTTCTCTTTGAAGATGCT
GGTGGTTAGGTGCTCTAGTATTCTCTATTTTTTTCTACTGTTTTTCCCCCTCTACTGTGC
TGTTACTCATTTATTCATTCACTCATCAAAAGGCACCATGAAAGAAAATCAGAGTGCAAT
GATGGATGGACAAGCCAGACTTTTTATCTACAACCTTAGAATGTAAAGTTAGCTAGGAAG
ACAGTCACAGAAAATATAATTAAAGGTCTATGAATATTATGAAGAGGAATTACAGAATGC
TTTGAAAGCTTATAAATGAGAACCTAATCTAGTTTTGGTGCTCAGAGAATATATTCCAAT
AAATAGTTTAGGCAGGAAGAATAAGTAGGTGTTGGCAAGAAAGGGATCCAGGATATTCCA
GGCACATGAAACACAGATGCAGA

The following amino acid sequence <SEQ ID NO. 213> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 93:

VCKWR* FP*YLQVIRK
IK*YANLKTC HSMNVN*FSL *RCWWLGALV FSIFFYCFSP STVLLLIYSF
THQKAP*KKI RVQ*WMDKPD FLSTTLECKV S*EDSHRKYN *RSMNIMKRN

BNSDOCID <WO 0166751A2 >

YRML*KLINE NLI*FWCSEN IFQ*IV*AGR ISRCWQERDP GYSRHMKHRCR

The following DNA sequence Seq-2320 <SEQ ID NO. 94> was identified in *H. sapiens*:

GAAAGAGGCTAGAACATGATTTACGTTCCTTCATACTCCTGCAAGAATGTTTAGAATCTG
AATCAAACAGACGAAAAAAAGCCAAGTTTGAGGCATATATTTTGCTGGCGAGGATCAAGG
CCGAGGTGGCAGCTAGCAGTGACTGCCCAATGTGGTAGGTGGATTCCTGATTCAGCAGCT
TCCTGGAGCAGACTTGGCATATTTCTGGATCATGGCAGAGTAGCCTGGGACTGAAGTCAG
CAGTATTAGCAGCAGATTCATAATCTGTCAGATTCCTGCATCTGTGGTGGTTGTTTACCT
GCTGAAGGCAAAGGCAGAGTGTTTCTGGGAGCTACTATTTGTTCCTGAGTATTAAGAATA
GAACTGTTCTTCCATTTCTTCCAATAAATTTGTTGGTTTTGAATACTTAAAATTTCTTGT
TATTTAAATAATCTAAAACTATGGCCCATAGGCCAAAGCTAGCTCACTGCCTGTTTTTGT
ATAGCTTACAAAATGGTTTTTACATTTTTTT

The following amino acid sequence <SEQ ID NO. 214> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 94:

KEART*FTFL HTPARMFRI* IKQTKKSQV*
GIYFAGEDQG RGGS*Q*LPN VVGGFLIQQL PGADLAYFWI MAE*PGTEVS
SISSRFIICQ IPASVVVVYL LKAKAECFWE LLFVPEY*E* NCSSISSNKF
VGFEYLKFLV I*II*NYGP* AKASSLPVFV *LTKWFLHFF

The following DNA sequence Seq-2321 <SEQ ID NO. 95> was identified in *H. sapiens*:

TCCCCAAAGATCAGATAATGTTCACAATATATAGTTTTTATGAGGATTAAATAAGATAAA
TAGTGCAAAGCACATAGAACACTTTCTGGTACATAATAATATGAAGGTGAAATAAATGAT
AGCATAGTAGGCTGTCTTAGCTGAGCACAAACTGATATTCAGTTTGTTATTGGTGAAACA
AGTGGATTTCGAGTGTAGGTACCACAGTTGAGTTCTACTGGAAATTTCTATAGTGAAATA
TTTACTAAATTAATTGCACATTAAAGAAAAGCTAAAGGCTGCAACTTGGAAATCAGTGAC
AATGCCAGGTAGTCAATGGACAGCAAGGATGTCTGAAGTGGACCATAATGTGGAAGAATG
CTTAAAAACACAAGCCTTCAAGGAAAATCAGCAGCTCTGGGCTTGGAGAAAATTTTTTAA
AGCATAGACATTTCTCCAAGGAGGAAGTAGTCTAATAAGAGAAGACAGATGATGGACAAA
CAAAAACTTGGATGCAATAAAGAATAAATGTAAGAGGTTCCACACTAGAAGGTGGGGAAG
TAATTAGTGGGTAAGTTTGATTAGGGGAATTTCAAAATCATGGACCTTTCATGGAATTCT
TTCTTGCTTTCAACTGTGTTGACCCATGCGTA

The following amino acid sequence <SEQ ID NO. 215> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 95:

RMGQHS*KQE RIP*KVHDFE IPLIKLTH*L LPHLLVWNLL HLFFIASKFL
FVHHLSSLIR LLPPWRNVYA LKNFLQAQSC *FSLKACVFK HSSTLWSTSD
ILAVH*LPGI VTDFQVAAFS FSLMCN*FSK YFTIEISSRT QLWYLHSKST
CFTNNKLNIS LCSAKTAYYA IIYFTFILLC TRKCSMCFAL FILFNPHKNY
IL*TLSDLWG

The following DNA sequence Seq-2322 <SEQ ID NO. 96> was identified in *H. sapiens*:

BNSDOCID <WO___0166751A2_I_>

AAGAGATATGAAATTAATCACACAGGAAATTGATATTTAACAAGCAATTATAAAGCAGTA
GATACATAATTTAATATACACCATCTATTTAAATGTCAACATAATTCTGTAGACTGCATA
ATATTAATGGTGTTTTAAATATGAATGCCAATATAGATATTATCAGAAAATAATAATTGT
ATAATATGTTTCTTTTTCACCAAGGAAATCAGTACAGGTGGAATGATAAGAAACAATAAA
ATAAACTATATGGTATGTGAATTGAAAATGTACAACCTAGTGGAAAGAATATGTGCTTTG
TAAACAAGGAGACATGGGAATATATTCAGGCTACATTTCCTTCATGTTCAAAATGTATAA
AGTTGAAGTAATAATGTTTATCTTACAAGATATTTGAAGATAAATTGAGTCCCTAGGCAG
TGAGAAGTGCAGGATCTGCATTCAGAAAGTTTAATATTGAGTCTGGTTTTTTCACCTGTT
CTTTGTCTGACTGTCCTATTCTTCATGTTTACCATTTATTTAATAGGGAAACGGAATTGT
ATTCATGGAATTTTTGTGGGGTTAAATAAAGACAAAGAACCTGGAATAAAGCTCCTGATC
ACATTACATGTTCAATAAATCATATGTATTTTTATCATTGTGGACACTCTCTGAAATTAT

The following amino acid sequence <SEQ ID NO. 216> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 96:

KRYEINHTGN *YLTSNYKAV DT*FNIHHLF KCQHNSVDCI ILMVF*I*MP
I*ILSENNNC IICFFFTKEI STGGMIRNNK INYMVCELKM YNLVERICAL
TRRHGNIFR LHFLHVQNV S*SNNVYLTR YLKIN*VPRQ *EVQDLHSES
LILSLVFSPV LCLTVLFFMF TIYLIGKRNC IHGIFVGLNK DKEPGIKLLI
TLHVQ*IICI FIIVDTL*NY

The following DNA sequence Seq-2323 <SEQ ID NO. 97> was identified in *H. sapiens*:

AATTCTATGGTCTTGAACAAACACACTCAATTAACTTAATACCTGAGAGAATACTCGTTT
TACATTTATCAAATCATAAGAGTGATATGCTAAACAGACTAGACAAGCAAATAAAGTTGC
TGACTTTATCTACAGTCACCGAATGCAAACTATCTGAGTTTACTAAATGTTTACTCAGTC
TAGTTAACTACTCTGCTAAGGATTATGTGTGAAAAGGACAGGCTTACATCATGCTGTTTT
GACCCAAGGTTCAAAGAAAGATCACATATGGAACTAGTATGCTCTTTGTATAATAAATTG
AAATCTTAGATTTTAAAAATCAAAATCTGATGGGTCCATTCCTCCAAGACACACAAATAG
CCAATAAGCACATAAA

The following amino acid sequence <SEQ ID NO. 217> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 97:

NSMVLNKHTQ LT*YLREYSF YIYQIIRVIC *TD*TSK*SC *LYLQSPNAN
YLSLLNVYSV *LTTLLRIMC EKDRLTSCCF DPRFKERSHM ELVCSLYNKL
KS*ILKIKI* WVHSSKTHK* PIST*

The following DNA sequence Seq-2324 <SEQ ID NO. 98> was identified in *H. sapiens*:

ACAGAATGAAGACAGTATGCCAGCACCTTTTTGGATATATACATCAGTAAATCTTGGACA
GCGTAAAGGGATAGCAACAGAGAGTTCTGATGCTGCCCCCTGCACCCACCCGTGGAGATG
GGGATGAATAATTAAAACCTTCGTATTTTGGCAGATGTGCAGACATTTTCACAAACCAAA
GCTATCAGTTAGTCAGTCGGGTTTCCCTTATTATTGCAGTGCTTCTTAATTCTTATATAT
ATACAATTATGTTTGGGGAAACTAAATAATAAAAACATTGTTGGGTAAAAATCAGAGTTT
TTTATAACCTCATCTGCTGATTCACTGACGAAGCTTCTCTTCAATACGGCCCTAGGACTT
CCCATCCCGTGATGGGAACCCACACTATACGTATATACCAAATACTCTATGTACAGACAT
GCATCACGCCATGATGCGGATACCTCCTGAGAAGTGCATTGTTAGGCAATTTTGTTACCG

TGTGAACATGGTAGAGAGCATGTACACAGACCTAGAAGGCATGGTCCAGGCACCCCTAGA
CTGTATGGCGTAGCCCATTGCTCCTAGGCTAGAAACCAGCACAGCACGTAACTATACTGA
ATACTGTGGACAGTTAAAATACAGTGATGAGTATTTGTGTATATAAACAGATCTAAACAC

The following amino acid sequence <SEQ ID NO. 218> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 98:

R MKTVCQHLFG
YIHQ*ILDSV KG*QQRVLML PPAPTRGDGD E*LKPSYFGR CADIFTNQSY
QLVSRVSLII AVLLNSYIYT IMFGETK**K HCWVKIRVFY NLIC*FTDEA
SLQYGPRTSH PVMGTHTIRI YQILYVQTCI TP*CGYLLRS ALLGNFVTV
TW*RACTQT* KAWSRHP*TV WRSPLLLG*K PAQHVTILNT VDS*NTVMSI
CVYKQI*T

The following DNA sequence Seq-2325 <SEQ ID NO. 99> was identified in *H. sapiens*:

CCCTTGAAACCTGCAGTCCTGCCTCAACATTTAATAACTCACGTCCAGTCTCATTTCACA
TAAATGCTTGTCCACTTTCTCTCTCCCAACACTGACTCCCAGACTTGAAATCATTTCTTT
GAAGCTCTTTCACTAAGGGTTCTCCAAATTAAGAACTTTAAAAAACATAACCACAACACC
ATTATCATACCTAGAAACCTACAATCATTCCTTAATATCATCAAATGTCTAGTGAGTATT
CAAAATTCCAGTTTGGTATTTTATTTTCTCTCAGTTAACATAGAATCACAATCAAAACAC
GGTTCGTTTATTGCATTCAGCTGACATGCTTCTCATGTCTCTCTCCACATTCAAACTCTC
CCTTGACGTTCTGTTTTTCCTGAATTCACGTGATAAAATAATGGATCTGTTTGTTGGGAG
TTTCCCATATTCTGGATCTTGCCAGCTCCATCTCTGTGGTGCCATTGAACACGTCCCCTG
GGTTCTCTAGATCTGCTATAATCAGGCAATTGGATCTAAGGCATTGGTTAGGTTCAGAGT
TGGATTTTTGGCAAGATTGCACCATTGATGGCTTCATGTATATGCACACAGAATGCCTGG
TGAGGCCCAGAGCATTGGTGTTAGGATGCTTCAGTGTTCAGGGAATATAGGCTGACTTGC
AAAGGTCCCCATCAGCTTCCCACCTAATACTTTTAGCAGCCATTAACAATCATTTCCCAG
ATCCTTTACATCTTTGAGT

The following amino acid sequence <SEQ ID NO. 219> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 99:

S KM*RIWEMIV NGC*KY*VGS
*WGPLQVSLY SLNTEAS*HQ CSGPHQAFCV HIHEAINGAI LPKIQL*T*P
MP*IQLPDYS RSREPRGRVQ WHHRDGAGKI QNMGNSQQTD PLFYHVNSGK
TERQGRV*MW RET*EACQLN AINEPCFDCD SMLTERK*NT KLEF*ILTRH
LMILRNDCRF LGMIMVLWLC FLKFLIWRTL SERASKK*FQ VWESVLGERK
WTSIYVK*DW T*VIKC*GRT AGFK

The following DNA sequence Seq-2326 <SEQ ID NO. 100> was identified in *H. sapiens*:

TCAGGAGGCAAGACTGTGGATGTAATTGCTGGAACTGAGGCAGCTATCTTGCAATGATGA
GGTGACAAGCATGAGGACAAGTAGACATGCCAAGGAAGGAAAAGCAGAAAAAAATAGAGC
CCAGCTTCTTGAGGAAATTGTTGAGCCGCTACACCAAGTCAGGAACATCTGTCTGCAGAC
TGATGGCTACAGGTGTATTATGATGCTTAAGCTACTGTTTAGTTGTCTGTTCATTGCATC
CTGGTTGATGCATTCAGTGAGTGAGGCAAGGAGTGAGCAACCTGACATCAAAGCTTGCTG
AGGACAGGTGACATGGACAGACAACTAGAATCATGACAGCTATCCAAAAAAGGATATCAC

BNSDOCID <WO__ 0166751A2_I_>

ATTTAACAAAAAACAGATTCGAATATGGTGGCTGTTTCTAATATGACTTAAATCCACAAT
GGTTTAAATAATGCAAAAATAAAAGAAATTTTGTGCAGGTTCCTGCCTTGTTTCTTGCCA
TTTGCTGTGTGTCCAACTCCTCTGATGAGGTCAGAATGTCTGATTTCCCACACCCAAGGA
AAGCATTTCTTGCCTTATTCCCTTCTTGACATCTTAAGAGCTTCAT

The following amino acid sequence <SEQ ID NO. 220> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 100:

EALKMS RRE*GKKCFP WVWEIRHSDL
IRGVGHTANG KKQGRNLHKL SFIFALFKPL WI*VILETAT IFESVFC*M
YPFLDSCHDS SCLSMSPVLS KL*CQVAHSL PHSLNASTRM Q*TDN*TVA
AS*YTCSHQS ADRCS*LGVA AQQFPQEAGL YFFLLFLPWH VYLSSCLSPH
HCKIAASVPA ITSTVLPP

The following DNA sequence Seq-2327 <SEQ ID NO. 101> was identified in *H. sapiens*:

ATGGGGCCCTCATGGAGTCATCACCCACTAATGGCCCACCTCTTAAATACTGTTGCACTG
GTACTTAAATTTCAAAGCTGATTTTAAAGGGAACACATATTCAAACCATAGCAAGCCTAT
TAAGAGCATTCTTAATTTCCATTTCAGTAGTTTTGATTTCAGGATTTTCTTTTGATTTTT
TTTCCTTATAGGTCTTCTCTCTCTGCTGACATTAATGTAAGAAAAATAAATATTCCATTA
GATATCTTAATAAGAAAAAACAAGTTTTCCATTAGATCTCTTAATACATTGAGCACAATC
ATTTTAAATATCTTTTCTGATAAATACAAGATCTGTGTTTTTCTATTCTGATCTTGATGA
TTGCTTGTCTATTCAGAATGCTTTCCTTTTCTATTTTTTTTTCTGTTTGCCTTTGGTATG
CCTTGTAATTTTCTGTTGTCAGCTGGACATGTTGTATCAGGTAATACGAATTGTGGTAAA
TAGGTCCCTAGTGTAAGGACTGATATGTTAATCTGGCTAAGTGTG

The following amino acid sequence <SEQ ID NO. 221> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 101:

WGPHG VITH*WPTS* ILLHWYLNFK
ADFKGNTYSN HSKPIKSILN FHFSSFDFRI FF*FFFLIGL LSLLTLM*EK
*IFH*IS**E KTSFPLDLLI H*AQSF*ISF LINTRSVFFY SDLDDCLSIQ
NAFLFYFFFC LPLVCLVIFC CQLDMLYQVI RIVVNRSLV* GLIC*SG*V

The following DNA sequence Seq-2328 SEQ ID NO. 102> was identified in *H. sapiens*:

TTTTTTTTGTAATGAATTTGAACACTGCTAGAGGAGTTTCTGATAAATTAATGTCATTTT
CAAATTTTAGTATATGTGCTGCCGAAGCGAGCACAAATTAATGTCATTTTCAAGTACAGC
CATCCCTCAGTATTCTCAGGGCACTGGTTCCAGGACCCCTGTGAATACCAAAACTCAAGG
ATGCTCAAGTCTCTTATATACAATGGTGTGATATTTGCATATAACCTGTTCACGTCCTTC
TGTATACTTTAAATCATCACTAGATTACTTATAATATTTAATATGTAAATGCTATGTAAA
TAGTTGTACTGTACTTTTAAAATTTGAATTTTTTAATGTTATTTTAAAATTTTTTTCTGA
ATACTTTCAATCAGCGGTTGGTTGAATCCAACCCATGGATACAGAGAGATGAGTATATTA
AAATTTAACCCACTTGATTCTTTCAACTTTTTGCCAGTGTTTTAGATTTTTACTATGGTA
TTTTAAAAATAGTATTTTTCTCCCACTACTGTTTTGGGTTCCTCAAGGTAAGGACTATCT
TGTTCACCTTTGTATCTTTAATAGCTGGTACAGTGTCTGGAACACAGTAGGTGAGCTCAG
TAAGTGGGGATATCCCAAATCTGGTGAAAACCTTCTAGATGACCTTGATGATTTGCTG

The following amino acid sequence <SEQ ID NO. 222> is the predicted

BNSDOCID <WO 0166751A2 >

amino acid sequence derived from the DNA sequence of SEQ ID NO. 102:

F FCNEFEHC*R SF**INVIFK F*YMCCRSEH
KLMSFSSTAI PQYSQGTGSR TPVNTKTQGC SSLLYTMV*Y LHITCSRPSV
YFKSSLDYL* YLICKCYVNS CTVLLKFEFF NVILKFFSEY FQSAVG*IQP
MDTER*VY*N LTHLILSTFC QCFRFLLWYF KNSIFLPLLF WVPQGKDYLV
HLCIFNSWYS VWNTVGELSK WGYPKSGENL LDDLDDLL

The following DNA sequence Seq-2329 <SEQ ID NO. 103> was identified in *H. sapiens*:

GAGCTTAGAGCCTCCAACAAAGGTAGGCATTAACAAAAAACATTACACAGTTATACTCAC
CATTACAGTAGAGCACAGCAGTTTAGAACGTGGGCACTGGGGTCTGCCCGGGTTCAAATT
CCAACTCTGCTACCAAATGGCTGTGTGACTTTGGACAAGTGACTTAACATTCCTCACTTC
AGTTTCCTCATCTATAAGATGCAGATAATTCTAGGTCCTACTTATTTACCCACCTATACA
ACTCATAGGGTTGCTATGAAAACCAAAAAACTTCCTATGTGTAAGTGCTAAGAACAGTCT
CTGCAACTCATAAACACTCAAAGGTTGCTGCTATTATTGTTGTTACCATCATTACTATTA
ATAATTTCAGAGGGAATCTAATCTACCTTTAGGCAAATGGAAGGTCAGGGAAAACTTTCT
TGAGAAAGGAACACATAAGCTAAGTCCTTAAGATAAATACAAATTAAACATGCCAAGAAA
AAAGGTGTCCAGCAGAGAAAAGAGCATATACAAAGCCCTGTGCTAAGAATGAGCTTGGCA
TGTGAAGGATCTGAAAAAGGGCCAGTGAAGCTAAGGCGC

The following amino acid sequence <SEQ ID NO. 223> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 103:

RLSFTGPFSD PSHAKLILST GLCICSFLCW
TPFFLACLIC IYLKDLAYVF LSQESFP*PS ICLKVD*IPS EIINSNDGNN
NNSSNL*VFM SCRDCS*HLH IGSFLVFIAT L*VV*VGK*V GPRIICIL*M
RKLK*GMLSH LSKVTQPFGS RVGI*TRADP SAHVLNCCAL L*W*V*LCNV
FC*CLPLLEA LS

The following DNA sequence Seq-2330 <SEQ ID NO. 104> was identified in *H. sapiens*:

CTTCTTTTTATAATAATTTTAAAAAGTCAAGTTTGAAAGCTCTGGTAGTTTACAATTTAT
CAGTGATAGGAACAAAATGTTAGCATAAAAACTTTGGAAGGCATTAAATATAATGGGAAT
TAGAGTTTGATTATGTCATGCTAATTTAATGAAAATGAATTAGTTTTAAAGAGTTTTAAA
CATAAGGGAAAATGTGTAACTAATATGAAATCCTGTATGTTTATTTGCTTCACTATGGTA
CAATTTTTACTATGTATTTGTATCCCATAACATCACTTTGTATGTCTTCAATATACAAAA
TAAAATTTATTTAAAATGAACATTTGATGAGCTCTAATGCGGAAAGACCTGCATAAAATT
AGTCAGTAC

The following amino acid sequence <SEQ ID NO. 224> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 104:

LLFIIILKSQ V*KLW*FTIY Q**EQNVSIK TLEGIKYNGN *SLIMSC*FN
ENELVLKSFK HKGKCVTNMK SCMFICFTMV QFLLCICIP* HHFVCLQYTK
*NLFKMNI** ALMRKDLHKI SQY

BNSDOCID <WO 0166751A2_I_>

The following DNA sequence Seq-2331 <SEQ ID NO. 105> was identified in *H. sapiens*:

TAACCAATGCTGAAAGCACACCTGTAAACAGCTCTGCATGTGATCATGCAGAGTCAGAAC
ACTGTACATTATATTTTGTTTGTAGAAATAGAATAGGATTAAACTGGTACAATTACAAAG
TAATTTGTCCAATGAGGAAAAGACACCTAAGTCTACAGTGCACTTGGAGACCTAGGCATG
ATGAAAAGGAAGGAACAGGACAGTTTTTTTCTTGCCAACT

The following amino acid sequence <SEQ ID NO. 225> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 105:

VGKKKTVLF
LPFHHA*VSK CTVDLGVFSS LDKLLCNCTS LILFYFYKQN IMYSVLTLHD
HMQSCLQVCF QHWL

The following DNA sequence Seq-2332 <SEQ ID NO. 106> was identified in *H. sapiens*:

AGGTTGGCCTCTGTTCTATACAGTTTACTTATACTTTGCTTGTAGTTCACTGTGATTTCT
TTTTTCTTCATTCATTCCTTCACTGGCTTAGGCTATAAACCTACCAGTCATCCCTAGTTC
TTTTCTTCCTGTAACTACTAATCATTTCCCTCTTCGTTCCCCTGAGCTGAATCATCACTC
CAGCCACTTCCAATTTAACAGTACATTCTTTAAAACATACAGTGATCTCATAGTTTGTCT
TCATCTCTGTGGAATCACATCTATATCTAACCTGGATTATCACAATAGCCTCCAAACTGA
CTTTGCTGTTTCCAAGACATTTGCCTCCCTGCTGTATATTTTCTGCCCAGGAGCTGTAAT
AACATTTTAAAAATATAAATCATATCAGGTCACTTCCCTGCTTAAAACTTTGCAATGGTC
TCAGTAAACTTAAAAAATATCCAAAGTTCTTAAAACGGCTTACATTATTTAGATTTTTCT
TTTCCAACTCATTTCCCAATCTTTTTCTTTTGACACTATTGCCTTCTCTTTACATCCTTG
TAACTATCCATCTAAAAGCATCTCTCCCACTAATCACTTTCAAACTATTCTATTTTTCAA
TATAATCTACCACTACCAGATACT

The following amino acid sequence <SEQ ID NO. 226> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 106:

GW PLFYTVYLYF ACSSL*FLFS SFIPSLA*AI NLPVIPSSFL
PVTTNHFPLR SPELNHHSSH FQFNSTFFKT YSDLIVCLHL CGITSISNLD
YHNSLQTDFA VSKTFASLLY IFCPGAVITF *KYKSYQVTS LLKTLQWSQ
T*KISKVLKT AYII*IFLFQ LISQSFSFDT IAFSLHPCNY PSKSISPTNH
FQTILFFNII YHYQI

The following DNA sequence Seq-2333 <SEQ ID NO. 107> was identified in *H. sapiens*:

TTTGTTTTTGTTTCTAAGAGAGAGCAGAGCTAAAAAGCCCATCCTTACCTCAGTAGACCA
ATGAGTGGTCTGATTCCATCTGGCTCTGCTGCTCAAATGGCAGTTGGGATGATAGTCATG
CTACAGACACATTTACCAACTAAGCAGTGCAGACAGTACTCTGCATTGGCCCAAATTTAC
CTAGGAACAAGCACAGGTGTGCTCAGATAAGGAAAATACCTTAGGTCAGGAGGGGGGGTG
AGCACATGGTTGGTAAAATAGAATTTAGTGAGTTAAAAAAAAAAACCAGCAAACCAACACA
AGACTCATAAGTACCCTATAGTATCTGCGGATGCCGTTACACGTCAAGTTAAACCACATC
TTCTCAGGATACAGGGGTGTTTTGCAGCTCTCACATTAACACAGATGTGTAACGTGGGTT
TCTCAGCCTATCAGAAATGGGGCAAGATAGGGTTATAATAAACAGCTTTTGTTTTTTTTG

BNSDOCID <WO 0166751A2_I_>

GCTCTGCCCTTACTAGGGGAGACTTCCAACC

The following amino acid sequence <SEQ ID NO. 227> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 107:

G WKSPLVRAEP KKTKAVYYNP ILPHF**AEK PTLHICVNVR
AAKHPCILRR CGLT*RVTAS ADTIGYL*VL CWFAGFFFNS LNSILPTMCS
PPLLT*GIFL I*AHLCLFLG KFGPMQSTVC TA*LVNVSVA *LSSQLPFEQ
QSQMESDHSL VY*GKDGLFS SALS*KQKQ

The following DNA sequence Seq-2334 <SEQ ID NO. 108> was identified in *H. sapiens*:

AATAATAATGTCAAGGATTATTGCAAGTATTAAGTAAGAAAATGAACATTACACTCAGAG
TAAACACTAGCATTTAGAAAATGTACAATAAATGATAGCAGCTCAGTTCATTATAATTAT
CATAGCCTTAAAGAAATAGTAGAAAGAAGAAAAACACTGAACTTGGGCCAAGCTGTGCTG
AAAGCTCATCTCTGCTACTTGTGAGTTGTGTGATTTTGGGTGATTTATAATCTTCGAGGG
CTTTTTTTTTCTTTGTCTGTAAAATGGCGTTAGTTTCACCTAATATCTACAAGTTATTAG
GAAAATTAAATGATATGCTAATCTAAAAACTTGCCATTCAATGAATGTTAATTAATTTTC
TCTTTGAAGATGCTGGTGGTTAGGTGCTCTAGTATTCTCTATTTTTTTCTACTGTTTTTC
CCCCTCTACTGTGCTGTTACTCATTTATTCATTCACTCATCAAAAGGCACCATGAAAGAA
AATCAGAGTGCAATGATGGATGGACAAGCCAGACTTTTTATCTACAACCTTAGAATGTAA
AGTTAGCTAGGAAGACAGTCACAGAAAATATAATTAAAGGTCTATGAATATTATGAAGAG
GAATTACAGAATGCTTTGAAAGCTTATAAATGAGAACCTAATC

The following amino acid sequence <SEQ ID NO. 228> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 108:

IIMSRI IASIK*ENEH YTQSKH*HLE NVQ*MIAAQF
IIIIIALKK* *KEEKH*TWA KLC*KLISAT CELCDFG*FI IFEGFFFLCL
*NGVSFT*YL QVIRKIK*YA NLKTCHSMNV N*FSL*RCWW LGALVFSIFF
YCFSPSTVLL LIYSFTHQKA P*KKIRVQ*W MDKPDFLSTT LECKVS*EDS
HRKYN*RSMN IMKRNYRML* KLINENLI

The following DNA sequence Seq-2335 <SEQ ID NO. 109> was identified in *H. sapiens*:

CTGGAAAGAGAGCTCTCTTGACCAGATTCATAAGTTCTTTGGGTACTTTTTGCCACCTGC
CATGTTATCAGAGACATCATTGCAAATTGCCAGTTGTTCTGCAACCACACAACTTTGTTT
CTTCTTTCTCCAGTTTCTATCACTCTTTTTGCTTTTTGGTCACTTACAGGATTTTTTTCC
CCCCAAGTCCAAGTGTTCCAAAATATCACATTTACACTCTTCTTATTGCCTTTCCAGCCA
CAGTCTGCTATATGGTATCAAAGTCAATGTCCCCTATATTTAGATTTAATGTCCTGCACC
CTACTTCTAGGTATTAATTTCTGCATTAGTTATGTATTACTGGACAACAAACTACCTCAA
ATGTAAGAGCTTCACATTATCATAATTGATATATATGTGAGCTAGAATAATTTTTTTTTA
AATCAGTTTTCCCTTGAACATCTCAGGCAGCAGCGTTCAGTGGAATGTGACTGTGTCGGA
A

The following amino acid sequence <SEQ ID NO. 229> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 109:

BNSDOCID <WO 0166751A2_I_>

LERELS*PDS *VLWVLFATC HVIRDIIANC QLFCNHTTLF LLSPVSITLF
AFWSLTGFFS PQVQVFQNIT FTLFLLPFQP QSAIWYQSQC PLYLDLMSCT
LLLGINFCIS YVLLDNKLPQ M*ELHIIIID IYVS*NNFFL NQFSLEHLRQ
QRSVECDCVG

The following DNA sequence Seq-2336 <SEQ ID NO. 110> was identified in *H. sapiens*:

AAACTTTTGTCGCAGGCTGATCCTAGGCTCAGAACAAGCCTAGCTAAGTGTTAAAAGAGT
CCCAACCCCAATTTGCAAAAGATAGGAGAGGTATGCTTGTGTGTGTACGTGTGTGTGTGT
GTGTGTGTGTGTGTGTGTGTGTGTGTTGGTGTTGTTTTTTAGCTCCTGGCATTCAAGGAA
ATCTCTGTCAAAACACTGGCTAAACACAAGCTGAAGAAACAGACACTTTGGTGACCACAA
AAAAACAATGAATAGTCTTTGCAAAAATAGCTTGGGAAAGTATAAAAACAAACATTACTA
CAGTCTTCAGAAATTAAAAAAAAAATGCTGAGGAAGAGAGAGAATCTGATTTCCAGACTTA
TCACATTATAATAGTCAAATGTCCAGTTTTCAACAGCAACAGCAAAATCACAAGTCAGAC
AAATGGGAAAAGATGGCCTATTCAAAGGAAAAAAAAAAACAAGTTGAAAAAACTGTGTCC
AAGGCAGCCCAACATTACACTTATTAGACAAAAAACTTTAAAATAGCTATCTTAAAGAGC
TAAGAGCAAAAATGGATGAGGACTAAAGTAAATTA

The following amino acid sequence <SEQ ID NO. 230> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 110:

*FTLVLI HFCS*LFKIA ILKFFV**V
CWAALDTVFS TCFFFSFE*A IFSHLSDL*F CCCC*KLDI* LL*CDKSGNQ
ILSLPQHFFL ISEDCSNVCF YTFPSYFCKD YSLFFCGHQS VCFFSLCLAS
VLTEISLNAR S*KTTPTHTH THTHTHTHTY THKHTSPIFC KLGLGLF*HL
CDKS

The following DNA sequence Seq-2346 <SEQ ID NO. 111> was identified in *H. sapiens*:

CGCGTCCCGGGCGTCCGTCGGGGTCCGAGGTCCCTCCCTCAGGGGAGTCCCCGCTCGGCA
GCGCTCTCGCGTTTCACGCAGCGGCCGGGGATCTGGGACAGGCGGGGCCCCGAGGCCGAG
CCTGGCTGCTGCCCAGCGGCCGGTGCAGGCCTCAAGCTGGGCCGGGCGGAGGGGAACCGG
CGAGTTGAAGCCCCGGGGCCGAAAGCCGGAGCCTGTGGCGGCCGCGGGGGTGGGGAGGGG
GGTGGGGCGGCTTCTTGGGCAGCGCCACACGGCGGCGCAGTGATGGATGTTAACAGCAGC
TGGCCACCCGGACCTCTACGGGCGCCTCTGCTCTTTCCTCCTGCCGGAGGTGGGGG

The following amino acid sequence <SEQID NO. 231> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 111:

AS RASVGVRGPS LRGVPARQRS RVSRSGRGSG
TGGAPRPSLA AAQRPVQASS WAGRRGTGEL KPRGRKPEPV AAAGVGRGVG
RLLGQRHTAA Q*WMLTAAGH PDLYGRLCSF LLPEVG

The following DNA sequence Seq-2347 SEQ ID NO. 112> was identified in *H. sapiens*:

TTGAGGATCCTGAGGGTGTTCTTTGCAGAGAAGGCAGGGGAGGTTGTGGAGGCCTGTCAG

ENSDOCID <WO 0166751A2 I>

ATGCTTTCACACACTCAAGGCCAGTACTCCTCTTCCCTCTCATAGATGAGAAATGATGGA
CATTCATGGGGTCCTTTCTCTGCGTGTGCCAGGTACCTCTGCAGACACCATTATATTTCT
TTCTGAGATCAACCTTGCAGAGTGTGCCTTGGTGTCATCCTCATCTTACAGGTGTGGAAG
CTGAGGCCTAATGAGGCCATGTGTCTTCCGTTCCCCTTATACACCATGGGACATGGGGCA
GAGCATAAGCTTGAACCCCGGTCTCTAGGTTTTTTCTACCACACAGTGCAGTGAGAGAC
ATGAAGGGGGTTGATGTGTATGGAATACATATACATGCACATCCAGCTATACTTTTAAAA
AAAATATTATTGGATGGGTCTGGGTTCTCTATTTTATAAGTGACACATACAACTATTGAA
CCCATGTGAGATTATAGCCAGGAGTGCATAAAAAACTGTCCTCAGAACAAGTTGAATGGG
AAGTTGGGTAAAAACGAATAAGGTTGAGTTCACTCCACAGCCCCACAGATGCAACTGATT
TAATTGA

The following amino acid sequence <SEQ ID NO. 232> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 112:

N *ISCICGAVE *TQPYSFLPN FPFNLF*GQF FMHSWL*SHM
GSIVVCVTYK IENPDPSNNI FFKSIAGCAC ICIPYTSTPF MSLTALCGRK
KPRDRGSSLC SAPCPMVYKG NGRHMASLGL SFHTCKMRMT PRHTLQG*SQ
KEI*WCLQRY LAHAEKGPHE CPSFLIYERE EEYWP*VCES I*QASTTSPA
FSAKNTLRIL

The following DNA sequence Seq-2348 <SEQ ID NO. 113> was identified in *H. sapiens*:

GGCATGGGGATACTCATGAAGTGAGTAAAGCCCCTACAGATGCCAGGACCATGTCTCCAA
AACCCCAACCCTCCCTGCTTCTGTGCCCAGGCTCCTGCCAGAGTCAGAAGATGGCAGTGG
TCACTGGGTGGAGACAAAGACAGCCAAGGAACCATCCCAGGTAGGCAAGAAGGCAACAGG
AGGTGGGACCAGGAGGGAGATGAGGCTTCAAGTTTCCAAGTCTTCCTTGTCCCATCAGAC
TTCACTTACAAAATACGAATTCAAAGACAGCTACTGAAAGTTGCAGGACAATGACCATGA
GCATTAAACTCCAAGTGTGGGGCCCGTTTGAGTACCAGCTACACTGATGACACACCCATG
TGCTTCTTTAGTAGTAAAATAGGAAATGAGGCTTCTCCAATTCTCTCCCCTCCCTGCACA
CAGGATTTTAACTCTGATGAAGTCCAGTTTATCTATTTTTGGAAGTGTGATTCTCCCACG
GTCTGATTCCATCACCTTCAGAAGCCCTTTATCATGGGAATGTTTCCAATCTGGGATTCA
GAGAGACTTACCTAATCCCATGGCTGGGAGCCACACAAT

The following amino acid sequence <SEQ ID NO. 233> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 113:

LCGSQPWD*V SLSESQIGNI PMIKGF*R*W
NQTVGESHFQ K*INWTSSEL KSCVQGGERI GEASFPILLL KKHMGVSSV
LVLKRAPHLE FNAHGHCPAT FSSCL*IRIL *VKSDGTRKT WKLEASSPSW
SHLLLPSCLP GMVPWLSLSP PSDHCHLLTL AGAWAQKQGG LGFWRHGPGI
CRGFTHFMSI PM

The following DNA sequence Seq-2349 <SEQ ID NO. 114> was identified in *H. sapiens*:

AAACATGGTATAGACTAAACACCTCCCAAAGATCACCTGCAATTTAGGTGCATTTCAGGG
TCTTTCTTTCTTGGAATCATCTTATTTAATAATGAATATCAGGTAAGGTGGCAAACCTTA
TCATTCAAAAATTTAAATAAATGTCTATTATCTATCCTGTTCCATTCTTGAAAATTATGA
TAACTCAAGAGGTAGGTATCTCAGGGAAAGAACACTGTGATGTGTGGCTGGAGCAAGAAA

BNSDOCID <WO 0166751A2_I_>

TGTGTATCTCTTGTTCAGTGTTGAGTTTTGGCTCGTAGAATAGAGACTGGCTCATAATAG
GTACTCAGATATCTGTTGAAATAACCCAGGAAGAGGTGTGATGGGGGGATTAGCAGCAGC
TAGTCATAAACTGCCTGAGCAGTATGTGGGAAAGTGCTGGCCCAGGAGATAGCTGGATAT
CTGGGAGCCTTTTCATCCCAGGAGGCTCTTCCTGGGGGCCTTCCCACTCAGCCATGGGAA
GCTGCTTCTCTCTCTATGAAGTTTAGACTTTCCTGTGCACCCAGAGGTATCTTTCAACAA
TCAGGAGCTGAGTGCTTAGACAAAGGGTGAGGTGAGCTTGGACAAAAATCAAGATGAATA
TCTGTGACTATGCACATACTTGGTACAGACACGTCCATATATGCCACAGACACAAATACA
TGGAGATTGAACT

The following amino acid sequence <SEQ ID NO. 234> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 114:

TW
YRLNTSQRSP AI*VHFRVFL SWNHLI***I SGKVANLIIQ KFK*MSIIYP
VPFLKIMITQ EVGISGKEHC DVWLEQEMCI SCSVLSFGS* NRDWLIIGTQ
ISVEITQEEV *WGD*QQLVI NCLSSMWESA GPGDSWISGS LFIPGGSSWG
PSHSAMGSCF SLYEV*TFLC TQRYLSTIRS *VLRQRVR*A WTKIKMNICD
YAHTWYRHVH ICHRHKYMEI E

The following DNA sequence Seq-2350 <SEQ ID NO. 115> was identified in *H. sapiens*:

CTTTATGCCTCCAAATTCCCATTTCTCACCCTCTCCTGACGTTTCGCCTTTCCCCACCCC
CTCCCCGTGGTGCTCCAAGCTCAGTGGGTGGCAGCACAGCACGATGGTTCAGGACAGTGT
CTCTGGAGGGTGCTCTGGGCCCGTCACTAACCAGCTGGGCGGCCCCAAGTGAGTCACATA
ACCTCTCTGTCTGCCTCATTATCTGTAAAAAGAGGATGTGGTAGCATTTGCCTAACAGCA
AATGTAACTGATAATTAATGCATATAAAATGCTTAGAATAGTGAAAAATGGTGTTCAAAG
AAGCATTCGTTGTTATTGTTGTGTTTCTATGGGGTGAGGTAGCCAGTAAAACCCAAGGTT
AACACCAGACTGTTTTCCTCTAGGAAATACAACAAACAAGCAAGCAGAAGACATGGATCC
TGAAGTTTCTTATGAGCAGGAGACTAGCACAGACCACTGTTCCTACCATTGGGAGGACAG
CACACCTGGCTGGCTGCCAGAGTGGGCCTTGGGGAGTAGGAAAAGCCAAGGGCTTAAGAG
ATGGAAGATCTCCTGGGTCACACCCAGGAGACTATTCACTAGCTGCCCACTGGACAATAA
ACACCAACTGAGGACCCAGGTGACACAA

The following amino acid sequence <SEQ ID NO. 235> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 115:

LCHL GPQLVFIVQW AASE*SPGCD
PGDLPSLKPL AFPTPQGPLW QPARCAVLPM VGTVVCASLL LIRNFRIHVF
CLLVCCIS*R KTVWC*PWVL LATSPHRNTT ITTNASLNTI FHYSKHFICI
NYQLHLLLGK CYHILFLQIM RQTERLCDSL GAAQLVSDGP RAPSRDTVLN
HRAVLPPTEL GAPRGGGGER RNVRRG*EMG IWRHK

The following DNA sequence Seq-2351 <SEQ ID NO. 116> was identified in *H. sapiens*:

CAGTCTCACTTAGTTAACTCATCAGAAAAATGCTGTCAATCAAGGCTTTTAGTAGGATAT
AATATGGCAGCCAACAGGCAAAGATGACCAATTTTAGGATATGCAATCTCCCAGCTTGTT
TTTCCCAAGGATGGCCCCAATAGCTCCCATCCCACATGCTCTTGACCCTGCCATGCTGCA
TCAGGAGATGGAGTCTAATTGCCCTCTCCTTGAATTTGTGCTGTCTTGATGACCTACTTG

ENSDOCID <WO 0166751A2 I

TTAATGACTGAATAAAATGAAAGTGTTGCTGCTTGAGTTTCGAGACAAAGTCAGTAAAGG
CCATGAAGCCTCTACCTGGTTCTCATGCAACATTCACTCCAGGGGAAGTCAACTGCCATG
TAATAAGTTTAATAATTCTGAGACCACTATGGTAAAGAGGCCACAGATAATTGCTCCTTT
AGGTAGTCCCAGCTGATCCCAGCTTTCATCCATCCTTCCAAGACATCAGACACGTCAGTG
GTCTTGGACTCTTCAGAATAACTATCCAGCAGCTGAACCACAGAATGACCTCATCTCATG
CTACAGGGAGCCAGAGAGTCACCCAGCCAAGCCCTGCCTGCCTA

The following amino acid sequence <SEQ ID NO. 236> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 116:

RQAG LGWVTLWLPV A*DEVILWFS
CWIVILKSPR PLTCLMSWKD G*KLGSAGTT *RSNYLWPLY HSGLRIIKLI
TWQLTSPGVN VA*EPGRGFM AFTDFVSKLK QQHFHFIQSL TSRSSRQHKF
KERAIRLHLL MQHGRVKSMW DGSYWGHPWE KQAATLHILK LVIFACWLPY
YILLKALIDS IFLMS*LSET

The following DNA sequence Seq-2352 <SEQ ID NO. 117> was identified in *H. sapiens*:

CTACTAAGAAAACAATTCTCTATGAAAGTCAGATGCTACAGTTCACTAATGCAGGATTAT
CTCATCTACCTGCCCCAGCAGGTGGGTCCTATAGTTTACCTTTAGAGATGAGAACAAACT
TGAAACAACATAAAGCATCTTGCAACTCTGGCTAATTTTTTTCTCCTCCTTATACTCACA
AAAGCTTTCTAGTTGACGGTATTTCTTCTGTCCTTGGCACGTGACAAAGACTTGAGGCCA
AAGTCTGCATGTGATGTCAGCCTCCGTGAAAGACTCATATCTCTTCTGCTCTCCATCAAT
AGGGGAGGGGGCACAGAGGTATCTGGGGAGTGTCTGGCGTTTAGCATCTTTGTACAGAGC
CAGTCTCAGTGGATGTAGCCTCAGGACTGTGCAGAGAAAATCACCTGGCTTATTCAGAAG
GGCATTAAGGACAGCAGTGGAAACCAATGGTGCCTACATAAGTCAGATTCTCCCTCTTGT
AACTCCAGAATAGGACCAAATCTCCCCTCACTCACTCAAAGCCCAAACAATAGTTCATGG
AGAAAAGAACAACCAACTCTTACACAATTGGGAAAAAACAGGTTCTCTATGCACACAAGA
GACTATTAAGCAGAAGCCACATTAGACTGTCCATTTCCTCTTTGCACCAGGGAAGTGAGT
AGGGCAGTCTGCAG

The following amino acid sequence <SEQ ID NO. 237> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 117:

ADCPTHFPGA KRKWTV*CGF CLIVSCVHRE
PVFSQLCKSW LFFSP*TIVW ALSE*GEIWS YSGVTRGRI* LM*APLVSTA
VLNALLNKPG DFLCTVLRLH PLRLALYKDA KRQTLPRYLC APSPIDGEQK
RYESFTEADI TCRLWPQVFV TCQGQKKYRQ LESFCEYKEE KKISQSCKML
YVVSSLFSSL KVNYRTHLLG QVDEIILH** TVASDFHREL FS**

The following DNA sequence Seq-2353 <SEQ ID NO. 118> was identified in *H. sapiens*:

CCAAAACTTCAAGGCATCATGACCTCTAACTTTCTTCACTAATGTGTTGATGTCTGTCAC
TGCTTAACAAGCAAAATGGCATCAGAAAGAGGGTGAACAAATAAAGGTATATTTAGGGCT
AATGATGAATTCGAGGTAAAGCACATCAATGTTTCCACCAAGGTTTTTGCTTCCAGTGTG
GTAGGGCAAAAAGATGTGAACTGAATTATTGGTACTCTCAAATTAAATGTATTCATTTTA
TTAATTCATTTAGCAACAGACATACACAGGTACATATACCCATATCCGTAGTTTCACTTA
TAAAGAAAAATTAAATCCACCCAACTGTTTTGTTTTCTGCAATATTTTTAACTTCTGTGA

BNSDOCID <WO__0166751A2_I_>

CTTTTTGTTTTTTCCATTGCTTTGAATCCACAATAGGTAGGTAGGAGAATTTGAAGCACC
ATTGAAATGAAGTATTCTAGAAAAGTATGCAGAAAGATAAAGAAAATGCATCCATCTCTA
GAAGTGCTTACATCTACTTAGCAAGTGTGAAACTCACAATGAGGATTTAGCCTGTTAGTA
TGGCACAGATTATAAATAGGAGAGTCGCTGTTATAATGTAATATAATTAACACAATTGTT
CTTGTTATAGAGCATGATAGTAGCTACCACCTGTC

The following amino acid sequence <SEQ ID NO. 238> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 118:

DRW*LLS CSITRTIVLI
ILHYNSDSPI YNLCHTNRLN PHCEPHTC*V DVSTSRDGCI FFIFLHTFLE
YFISMVLQIL LPTYCGFKAM EKTKSHRS*K YCRKQNSWVD LIFLYK*NYG
YGYMYLCMSV AK*INKMNTF NLRVPIIQFT SFCPTTLEAK TLVETLMCFT
SNSSLALNIP LFVHPLSDAI LLVKQ*QTST H**RKLEVMM P*SF

The following DNA sequence Seq-2354 <SEQ ID NO. 119> was identified in *H. sapiens*:

ACAACTTGGCTTTAGCCATGGATTCCAGTGATCAGAGCAGCCTGCAAAAATAACTTAAAT
ATTAATTGTTTATTGATTAAATATTTAACAGAATTGGATCATCATTTGGTCTCTGGCCCA
GCATATCAGTGGTAGGAGTTAATCAAAAGGATCATTTGCCCCAGAAGAGTGGCTTTCAAA
TTTAGCATGCATTGGAATCCCCCTGGAGGGCTTGTTAACACAGATTATTGAACTCTACCC
CGAGAGTTTCTGGTTCAGTAGGTCTTGGGTTGGCTTGAGAATTTGCATTTCTAGCAAACT
TTCAGGTGATGCTGATGCTGCTGGTCCAGGGACCACGCTTTGAGTGAGAACCACGGGACG
AGAGAAACCACTGAAGAGCAGAGATTCATTTTGAAGACTACACCATAGGAAGGAGGCAGA
AAGTAGAAAGAAGCACTCCACTGCATAAAGCTGAAACTGGCATCCAGGAATGAGAGATAC
CAGGCAAGCTTTGGATGATTACAGGAAATAACTTCTCAAAGGTAAAAAATGAAGTCAGAT
CTCCTTACACCTATAGTAGCTTTTTTAAAGTTCCCATTTCATCAAGAATCAAGACAAGGA
TCATAAAGGAAATTGTCTTTGAGGCTGCATGCCCTACCTGATTGCTCTTGAACTGGAACT
CAG

The following amino acid sequence <SEQ ID NO. 239> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 119:

*VPVQEQS GRACSLKDNF
LYDPCLDS** NGNFKKATIG VRRSDFIFYL *EVISCNHPK LAWYLSFLDA
SFSFMQWSAS FYFLPPSYGV VFKMNLCSSV VSLVPWFSLK AWSLDQQHQH
HLKVC*KCKF SSQPKTY*TR NSRGRVQ*SV LTSPPGGFQC MLNLKATLLG
QMILLINSYH *YAGPETK** SNSVKYLINK QLIFKLFLQA ALITGIHG*S
QV

The following DNA sequence Seq-2355 <SEQ ID NO. 120> was identified in *H. sapiens*:

TTATGTTCAGAAATTATTTCTTCTGCATGACCTAGTCTACTGTGAAAGCCCTCAATTGTA
TTTTTTATTTCTTTCTTTGACTTCTTCACTTCCATGATTTCTCTTTGGTTTCTTTACATC
TATCTCTTTGTGGAATTTCTCATTCAAATCCTGATTTGTTTTCCTTATTTCTTTGTGTAG
TTTATCTGTTTTCTCTTATATCTCATTGAGTTTCTTTAATATTATTATTTTGAATTTCTT
TCAGACATTTTATAAATGTTTTTTGGATCTTTTACTTGAGAGTTATTGTGCTCCTTTAGA
AATGCCATGTTTCCTTGTTTTCTCATGTTTCTTATGTTCTTAAGTTGGTATCTGTGTATT

ENSDOCID <WO 0166751A2_I_>

TGGTGTGACAGTTGCTTCTCCTAGGTTTTTGGATTGGCTTTTGTAGGGAGAGGCTTTTTC
CTGTAGATATAGCTGTAGTGTTAGTTGCATAGAGTACTTTGGTTTTGATCCAAGGTGGGC
ACAGTATTATAGGCCCCATAGGATTTCTCCTGCTGTAAACAGTGTGAGTGGTGTCTGTGA
GCTCCTCAGTGGCTTAACAAC

The following amino acid sequence <SEQ ID NO. 240> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 120:

C*ATEELT DTTHTVYSRR
NPMGPIILCP PWIKTKVLYA TNTTAISTGK SLSLQKPIQK PRRSNCHTKY
TDTNLRT*ET *ENKETWHF* RSTITLK*KI QKTFIKCLKE IQNNNIKETQ
*DIRENR*TT QRNKENKSGF E*EIPQRDRC KETKEKSWK* RSQRKK*KIQ
LRAFTVD*VM QKK*FLNI

EXAMPLE 2: CLONING OF nGPCR-x

cDNAs may be sequenced directly using an AB1377 or ABI373A fluorescence-based sequencer (Perkin Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM Ready Dye-Deoxy Terminator kit with Taq FS polymerase. Each ABI cycle sequencing reaction contains about 0.5µg of plasmid DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9600 thermocycler. Extension products are purified using Centriflex gel filtration (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 1500 x g for 4 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 5µl of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for three min and loaded into the gel sample wells for sequence analysis by the ABI377 sequencer. Sequence analysis is performed by importing ABI373A files into the Sequencher program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

To isolate a cDNA clone encoding full length nGPCR, a DNA fragment corresponding to a nucleotide sequence selected from the group consisting of SEQ ID

BNSDOCID <WO__0166751A2_I_>

NO:1 to SEQ ID NO:120, or a portion thereof, can be used as a probe for hybridization screening of a phage cDNA library. The DNA fragment is amplified by the polymerase chain reaction (PCR) method. The PCR reaction mixture of 50µl contains polymerase mixture (0.2mM dNTPs, 1x PCR Buffer and 0.75µl Expand High Fidelity Polymerase (Roche Biochemicals)), 1µg of 3206491 plasmid, and 50pmoles of forward primer and 50pmoles of reverse primer. The primers are preferably 10 to 25 nucleotides in length and are determined by procedures well known to those skilled in the art. Amplification is performed in an Applied Biosystems PE2400 thermocycler, using the following program: 95°C for 15 seconds, 52°C for 30 seconds and 72°C for 90 seconds; repeated for 25 cycles. The amplified product is separated from the plasmid by agarose gel electrophoresis, and purified by Qiaquick gel extraction kit (Qiagen).

A lambda phage library containing cDNAs cloned into lambda ZAPII phage-vector is plated with E. coli XL-1 blue host, on 15 cm LB-agar plates at a density of 50,000 pfu per plate, and grown overnight at 37°C; (plated as described by Sambrook *et al.*, *supra*). Phage plaques are transferred to nylon membranes (Amersham Hybond NJ), denatured for 2 minutes in denaturation solution (0.5 M NaOH, 1.5 M NaCl), renatured for 5 minutes in renaturation solution (1 M Tris pH 7.5, 1.5 M NaCl), and washed briefly in 2xSSC (20x SSC: 3 M NaCl, 0.3 M Na-citrate). Filter membranes are dried and incubated at 80°C for 120 minutes to cross link the phage DNA to the membranes.

The membranes are hybridized with a DNA probe prepared as described above. A DNA fragment (25ng) is labeled with α-^{32}P-dCTP (NEN) using Rediprime random priming (Amersham Pharmacia Biotech), according to the manufacturer's instructions. Labeled DNA is separated from unincorporated nucleotides by S200 spin columns (Amersham Pharmacia Biotech), denatured at 95°C for 5 minutes and kept on ice. The DNA-containing membranes (above) are pre-hybridized in 50ml ExpressHyb (Clontech) solution at 68°C for 90 minutes. Subsequently, the labeled DNA probe is added to the hybridization solution, and the probe is left to hybridize to the membranes at 68°C for 70 minutes. The membranes are washed five times in 2x SSC, 0.1% SDS at 42°C for 5 minutes each, and finally washed 30 minutes in 0.1x SSC, 0.2% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with an intensifying screen at –80°C for 16 hours. One positive colony is isolated from the plates,

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and re-plated with about 1000 pfu on a 15 cm LB plate. Plating, plaque lift to filters and hybridization are performed as described above. About four positive phage plaques are isolated form this secondary screening.

cDNA containing plasmids (pBluescript SK-) are rescued from the isolated phages by in vivo excision by culturing XL-1 blue cells co-infected with the isolated phages and with the Excision helper phage, as described by the manufacturer (Stratagene). XL-blue cells containing the plasmids are plated on LB plates and grown at 37°C for 16 hours. Colonies (18) from each plate are replated on LB plates and grown. One colony from each plate is stricken onto a nylon filter in an ordered array, and the filter is placed on a LB plate to raise the colonies. The filter is then hybridized with a labeled probe as described above. About three positive colonies are selected and grown up in LB medium. Plasmid DNA is isolated from the three clones by Qiagen Midi Kit (Qiagen) according to the manufacturer's instructions. The size of the insert is determined by digesting the plasmid with the restriction enzymes NotI and SalI, which establishes an insert size. The sequence of the entire insert is determined by automated sequencing on both strands of the plasmids.

EXAMPLE 3: SUBCLONING OF THE CODING REGION OF nGPCR-X VIA PCR

Additional experiments may be conducted to subclone the coding region of nGPCR and place the isolated coding region into a useful vector. Two additional PCR primers are designed based on the coding region of nGPCR, corresponding to either end. To protect against exonucleolytic attack during subsequent exposure to enzymes, *e.g.*, Taq polymerase, primers are routinely synthesized with a protective run of nucleotides at the 5' end that were not necessarily complementary to the desired target.

PCR is performed in a 50µl reaction containing 34µl H_2O, 5 µl 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5µl 15mM $MgSO_4$, 2µl dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10 mM), 3µl genomic phage DNA (0.25µg/µl), 0.3µl Primer 1 (1µg/µl), 0.3µl Primer 2 (1µg/µl), 0.4µl High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction was started with 1 cycle of 94°C for 2 minutes; followed by 25 cycles at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1.3 minutes.

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The contents from the PCR reaction are loaded onto a 2% agarose gel and fractionated. The DNA band of expected size is excised from the gel, placed in a GenElute Agarose spin column (Supelco) and spun for 10 minutes at maximum speed in a microfuge. The eluted DNA is precipitated with ethanol and resuspended in 6µl H_2O for ligation.

The PCR-amplified DNA fragment containing the coding region is cloned into pCR2.1 using a protocol standard in the art. In particular, the ligation reaction consists of 6µl of GPCR DNA, 1µl 10X ligation buffer, 2µl pCR2.1 (25ng/µl, Invitrogen), and 1µl T4 DNA ligase (Invitrogen). The reaction mixture is incubated overnight at 14°C and the reaction is then stopped by heating at 65°C for 10 minutes. Two microliters of the ligation reaction are transformed into One Shot cells (Invitrogen) and plated onto ampicillin plates. A single colony containing a recombinant pCR2.1 bearing an insert is used to inoculate a 5ml culture of LB medium. Plasmid DNA is purified using the Concert Rapid Plasmid Miniprep System (GibcoBRL) and sequenced. Following confirmation of the sequence, a 50 ml culture of LB medium is inoculated with the transformed One Shot cells, cultured, and processed using a Qiagen Plasmid Midi Kit to yield purified pCR-GPCR.

EXAMPLE 4: HYBRIDIZATION ANALYSIS TO DEMONSTRATE nGPCR-X EXPRESSION IN BRAIN

The expression of nGPCR-x in mammals, such as the rat, may be investigated by *in situ* hybridization histochemistry. To investigate expression in the brain, for example, coronal and sagittal rat brain cryosections (20µm thick) are prepared using a Reichert-Jung cryostat. Individual sections are thaw-mounted onto silanized, nuclease-free slides (CEL Associates, Inc., Houston, TX), and stored at -80°C. Sections are processed starting with post-fixation in cold 4% paraformaldehyde, rinsed in cold phosphate-buffered saline (PBS), acetylated using acetic anhydride in triethanolamine buffer, and dehydrated through a series of alcohol washes in 70%, 95%, and 100% alcohol at room temperature. Subsequently, sections are delipidated in chloroform, followed by rehydration through successive exposure to 100% and 95% alcohol at room temperature. Microscope slides containing processed cryosections are allowed to air dry prior to hybridization. Other tissues may be assayed in a similar fashion.

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A nGPCR-x-specific probe is generated using PCR. Following PCR amplification, the fragment is digested with restriction enzymes and cloned into pBluescript II cleaved with the same enzymes. For production of a probe specific for the sense strand of nGPCR-x, the nGPCR-x clone in pBluescript II is linearized with a suitable restriction enzyme, which provides a substrate for labeled run-off transcripts (*i.e.*, cRNA riboprobes) using the vector-borne T7 promoter and commercially available T7 RNA polymerase. A probe specific for the antisense strand of nGPCR-x is also readily prepared using the nGPCR-x clone in pBluescript II by cleaving the recombinant plasmid with a suitable restriction enzyme to generate a linearized substrate for the production of labeled run-off cRNA transcripts using the T3 promoter and cognate polymerase. The riboprobes are labeled with [^{35}S]-UTP to yield a specific activity of about 0.40 x 10^6 cpm/pmol for antisense riboprobes and about 0.65 x 10^6 cpm/pmol for sense-strand riboprobes. Each riboprobe is subsequently denatured and added (2 pmol/ml) to hybridization buffer which contained 50% formamide, 10% dextran, 0.3 M NaCl, 10 mM Tris (pH 8.0), 1 mM EDTA, 1X Denhardt's Solution, and 10 mM dithiothreitol. Microscope slides containing sequential brain cryosections are independently exposed to 45 µl of hybridization solution per slide and silanized cover slips are placed over the sections being exposed to hybridization solution. Sections are incubated overnight (15-18 hours) at 52°C to allow hybridization to occur. Equivalent series of cryosections are exposed to sense or antisense nGPCR-x-specific cRNA riboprobes.

Following the hybridization period, coverslips are washed off the slides in 1X SSC, followed by RNase A treatment involving the exposure of slides to 20 µg/ml RNase A in a buffer containing 10mM Tris-HCl (pH 7.4), 0.5M EDTA, and 0.5M NaCl for 45 minutes at 37°C. The cryosections are then subjected to three high-stringency washes in 0.1 X SSC at 52°C for 20 minutes each. Following the series of washes, cryosections are dehydrated by consecutive exposure to 70%, 95%, and 100% ammonium acetate in alcohol, followed by air drying and exposure to Kodak BioMax™ MR-1 film. After 13 days of exposure, the film is developed. Based on these results, slides containing tissue that hybridized, as shown by film autoradiograms, are coated with Kodak NTB-2 nuclear track emulsion and the slides are stored in the dark for 32 days. The slides are then developed and counterstained with hematoxylin. Emulsion-coated sections are analyzed

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microscopically to determine the specificity of labeling. The signal is determined to be specific if autoradiographic grains (generated by antisense probe hybridization) are clearly associated with cresyl violate-stained cell bodies. Autoradiographic grains found between cell bodies indicates non-specific binding of the probe.

As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. Expression of nGPCR-x in the brain provides an indication that modulators of nGPCR-x activity have utility for treating neurological disorders, including but not limited to, mental disorder, affective disorders, ADHD/ADD (*i.e.*, Attention Deficit-Hyperactivity Disorder/Attention Deficit Disorder), and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, and senile dementia. Some other diseases for which modulators of nGPCR-x may have utility include depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-x modulators, including nGPCR-x ligands and anti-nGPCR-x antibodies, to treat individuals having such disease states is intended as an aspect of the invention.

EXAMPLE 5: TISSUE EXPRESSION PROFILING

A PCR-based system (RapidScan™ Gene Expression Panel, OriGene Technologies, Rockville, MD) may be used to generate a comprehensive expression profile of the putative nGPCR-x in human tissue, and in human brain regions. The RapidScan Expression Panel is comprised of first-strand cDNAs from various human tissues and brain regions that are serially diluted over a 4-log range and arrayed into a multi-well PCR plate. Human tissues in the array may include: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, and fetal liver.

Expression of nGPCR-x in various tissues is detected using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a predetermined size fragment in the presence of the appropriate cDNA.

PCR is performed in a 50µl reaction containing 34µl H_2O, 5µl 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5µl 15mM $MgSO_4$, 2µl

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dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10mM), 0.3µl forward primer (1µg/µl), 0.3µl reverse primer (1µg/µl), 0.4µl High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction mixture is added to each well of the PCR plate. The plate is placed in a MJ Research PTC100 thermocycler, and is then exposed to the following cycling parameters: Pre-soak 94°C for 3 min; denaturation at 94°C for 30 seconds; annealing at primer 57°C for 45 seconds; extension 72°C for 2 minutes; for 35 cycles. PCR productions are then separated and analyzed by electrophoresis on a 1.2% agarose gel stained with ethidium bromide.

The 4-log dilution range of cDNA deposited on the plate ensures that the amplification reaction is within the linear range and, hence, facilitates semi-quantitative determination of relative mRNA accumulation in the various tissues or brain regions examined.

EXAMPLE 6: NORTHERN BLOT ANALYSIS

Northern blots are performed to examine the expression of nGPCR-x mRNA. The sense orientation oligonucleotide and the antisense-orientation oligonucleotide, described above, are used as primers to amplify a portion of the GPCR-x cDNA sequence selected from the group consisting of SEQ ID NO:1 to SEQ IDNO:120.

Multiple human tissue northern blots from Clontech (Human II # 7767-1) are hybridized with the probe. Pre-hybridization is carried out at 42 C for 4 hours in 5xSSC, 1X Denhardt's reagent, 0.1% SDS, 50% formamide, 250 mg/ml salmon sperm DNA. Hybridization is performed overnight at 42°C in the same mixture with the addition of about $1.5x10^6$ cpm/ml of labeled probe.

The probe is labeled with α-^{32}P-dCTP by Rediprime™ DNA labeling system (Amersham Pharmacia), purified on Nick Column™ (Amersham Pharmacia) and added to the hybridization solution. The filters are washed several times at 42°C in 0.2x SSC, 0.1% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with intensifying screen at –80°C.

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EXAMPLE 7: RECOMBINANT EXPRESSION OF nGPCR-X IN EUKARYOTIC HOST CELLS

A. Expression of nGPCR-x in Mammalian Cells

To produce nGPCR-x protein, a nGPCR-x-encoding polynucleotide is expressed in a suitable host cell using a suitable expression vector and standard genetic engineering techniques. For example, the nGPCR-x-encoding sequence described in Example 1 is subcloned into the commercial expression vector pzeoSV2 (Invitrogen, San Diego, CA) and transfected into Chinese Hamster Ovary (CHO) cells using the transfection reagent FuGENE6™ (Boehringer-Mannheim) and the transfection protocol provided in the product insert. Other eukaryotic cell lines, including human embryonic kidney (HEK 293) and COS cells, are suitable as well. Cells stably expressing nGPCR-x are selected by growth in the presence of 100μg/ml zeocin (Stratagene, LaJolla, CA). Optionally, nGPCR-x may be purified from the cells using standard chromatographic techniques. To facilitate purification, antisera is raised against one or more synthetic peptide sequences that correspond to portions of the nGPCR-x amino acid sequence, and the antisera is used to affinity purify nGPCR-x. The nGPCR-x also may be expressed in-frame with a tag sequence (*e.g.*, polyhistidine, hemagluttinin, FLAG) to facilitate purification. Moreover, it will be appreciated that many of the uses for nGPCR-x polypeptides, such as assays described below, do not require purification of nGPCR-x from the host cell.

B. Expression of nGPCR-x in HEK-293 cells

For expression of nGPCR-x in mammalian cells HEK293 (transformed human, primary embryonic kidney cells), a plasmid bearing the relevant nGPCR-x coding sequence is prepared, using vector pSecTag2A (Invitrogen). Vector pSecTag2A contains the murine IgK chain leader sequence for secretion, the c-myc epitope for detection of the recombinant protein with the anti-myc antibody, a C-terminal polyhistidine for purification with nickel chelate chromatography, and a Zeocin resistant gene for selection of stable transfectants. The forward primer for amplification of this GPCR cDNA is determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce the *HindIII* cloning site and nucleotides matching the GPCR sequence. The reverse primer is also determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce an *XhoI* restriction site for cloning and nucleotides

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corresponding to the reverse complement of the nGPCR-x sequence. The PCR conditions are 55°C as the annealing temperature. The PCR product is gel purified and cloned into the *HindIII-XhoI* sites of the vector.

The DNA is purified using Qiagen chromatography columns and transfected into HEK-293 cells using DOTAP™ transfection media (Boehringer Mannheim, Indianapolis, IN). Transiently transfected cells are tested for expression after 24 hours of transfection, using western blots probed with anti-His and anti-nGPCR-x peptide antibodies. Permanently transfected cells are selected with Zeocin and propagated. Production of the recombinant protein is detected from both cells and media by western blots probed with anti-His, anti-Myc or anti-GPCR peptide antibodies.

C. Expression of nGPCR-x in COS cells

For expression of the nGPCR-x in COS7 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 can be cloned into vector p3-CI. This vector is a pUC18-derived plasmid that contains the HCMV (human cytomegalovirus) promoter-intron located upstream from the bGH (bovine growth hormone) polyadenylation sequence and a multiple cloning site. In addition, the plasmid contains the dhrf (dihydrofolate reductase) gene which provides selection in the presence of the drug methotrexane (MTX) for selection of stable transformants.

The forward primer is determined by routine procedures and preferably contains a 5' extension which introduces an *XbaI* restriction site for cloning, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120. The reverse primer is also determined by routine procedures and preferably contains 5'- extension of nucleotides which introduces a *SalI* cloning site followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120. The PCR consists of an initial denaturation step of 5 min at 95°C 30 cycles of 30 sec denaturation at 95°C, 30 sec annealing at 58°C and 30 sec extension at 72°C, followed by 5 min extension at 72°C. The PCR product is gel purified and ligated into the *XbaI* and *SalI* sites of vector p3-CI. This construct is transformed into *E. coli* cells for amplification and DNA purification. The DNA is purified with Qiagen chromatography columns and transfected

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into COS 7 cells using Lipofectamine™ reagent from BRL, following the manufacturer's protocols. Forty-eight and 72 hours after transfection, the media and the cells are tested for recombinant protein expression.

nGPCR-x expressed from a COS cell culture can be purified by concentrating the cell-growth media to about 10 mg of protein/ml, and purifying the protein by, for example, chromatography. Purified nGPCR-x is concentrated to 0.5 mg/ml in an Amicon concentrator fitted with a YM-10 membrane and stored at -80°C.

D. Expression of nGPCR-x in Insect Cells

For expression of nGPCR-x in a baculovirus system, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 can be amplified by PCR. The forward primer is determined by routine procedures and preferably contains a 5' extension which adds the *NdeI* cloning site, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120. The reverse primer is also determined by routine procedures and preferably contains a 5' extension which introduces the *KpnI* cloning site, followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120.

The PCR product is gel purified, digested with *NdeI* and *KpnI*, and cloned into the corresponding sites of vector pACHTL-A (Pharmingen, San Diego, CA). The pAcHTL expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV), and a 6XHis tag upstream from the multiple cloning site. A protein kinase site for phosphorylation and a thrombin site for excision of the recombinant protein precede the multiple cloning site is also present. Of course, many other baculovirus vectors could be used in place of pAcHTL-A, such as pAc373, pVL941 and pAcIM1. Other suitable vectors for the expression of GPCR polypeptides can be used, provided that the vector construct includes appropriately located signals for transcription, translation, and trafficking, such as an in-frame AUG and a signal peptide, as required. Such vectors are described in Luckow *et al.*, Virology 170:31-39, among others.

The virus is grown and isolated using standard baculovirus expression methods, such as those described in Summers *et al.* (A Manual of Methods for Baculovirus Vectors

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and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987)).

In a preferred embodiment, pAcHLT-A containing nGPCR-x gene is introduced into baculovirus using the "BaculoGold™" transfection kit (Pharmingen, San Diego, CA) using methods established by the manufacturer. Individual virus isolates are analyzed for protein production by radiolabeling infected cells with ^{35}S-methionine at 24 hours post infection. Infected cells are harvested at 48 hours post infection, and the labeled proteins are visualized by SDS-PAGE. Viruses exhibiting high expression levels can be isolated and used for scaled up expression.

For expression of a nGPCR-x polypeptide in a Sf9 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 can be amplified by PCR using the primers and methods described above for baculovirus expression. The nGPCR-x cDNA is cloned into vector pAcHLT-A (Pharmingen) for expression in Sf9 insect. The insert is cloned into the *NdeI* and *KpnI* sites, after elimination of an internal *NdeI* site (using the same primers described above for expression in baculovirus). DNA is purified with Qiagen chromatography columns and expressed in Sf9 cells. Preliminary Western blot experiments from non-purified plaques are tested for the presence of the recombinant protein of the expected size which reacted with the GPCR-specific antibody. These results are confirmed after further purification and expression optimization in HiG5 cells.

EXAMPLE 8: INTERACTION TRAP/TWO-HYBRID SYSTEM

In order to assay for nGPCR-x-interacting proteins, the interaction trap/two-hybrid library screening method can be used. This assay was first described in Fields *et al.*, *Nature,* **1989**, *340*, 245, which is incorporated herein by reference in its entirety. A protocol is published in Current Protocols in Molecular Biology 1999, John Wiley & Sons, NY, and Ausubel, F. M. *et al.* 1992, Short protocols in molecular biology, Fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety. Kits are available from Clontech, Palo Alto, CA (Matchmaker Two-Hybrid System 3).

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A fusion of the nucleotide sequences encoding all or partial nGPCR-x and the yeast transcription factor GAL4 DNA-binding domain (DNA-BD) is constructed in an appropriate plasmid (*i.e.*, pGBKT7) using standard subcloning techniques. Similarly, a GAL4 active domain (AD) fusion library is constructed in a second plasmid (*i.e.*, pGADT7) from cDNA of potential GPCR-binding proteins (for protocols on forming cDNA libraries, see Sambrook *et al.* 1989, Molecular cloning: a laboratory manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY), which is incorporated herein by reference in its entirety. The DNA-BD/nGPCR-x fusion construct is verified by sequencing, and tested for autonomous reporter gene activation and cell toxicity, both of which would prevent a successful two-hybrid analysis. Similar controls are performed with the AD/library fusion construct to ensure expression in host cells and lack of transcriptional activity. Yeast cells are transformed (*ca.* 105 transformants/mg DNA) with both the nGPCR-x and library fusion plasmids according to standard procedures (Ausubel *et al.*, 1992, Short protocols in molecular biology, fourth edition, Greene and Wiley-interscience, NY, which is incorporated herein by reference in its entirety). *In vivo* binding of DNA-BD/nGPCR-x with AD/library proteins results in transcription of specific yeast plasmid reporter genes (*i.e.*, lacZ, HIS3, ADE2, LEU2). Yeast cells are plated on nutrient-deficient media to screen for expression of reporter genes. Colonies are dually assayed for β-galactosidase activity upon growth in Xgal (5-bromo-4-chloro-3-indolyl-β-D-galactoside) supplemented media (filter assay for β-galactosidase activity is described in Breeden *et al.,* Cold Spring Harb. Symp. Quant. Biol., 1985, 50, 643, which is incorporated herein by reference in its entirety). Positive AD-library plasmids are rescued from transformants and reintroduced into the original yeast strain as well as other strains containing unrelated DNA-BD fusion proteins to confirm specific nGPCR-x/library protein interactions. Insert DNA is sequenced to verify the presence of an open reading frame fused to GAL4 AD and to determine the identity of the nGPCR-x-binding protein.

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EXAMPLE 9: MOBILITY SHIFT DNA-BINDING ASSAY USING GEL ELECTROPHORESIS

A gel electrophoresis mobility shift assay can rapidly detect specific protein-DNA interactions. Protocols are widely available in such manuals as Sambrook *et al.* 1989, *Molecular cloning: a laboratory* manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY and Ausubel, F. M. *et al.*, 1992, Short Protocols in Molecular Biology, fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety.

Probe DNA(<300 bp) is obtained from synthetic oligonucleotides, restriction endonuclease fragments, or PCR fragments and end-labeled with ^{32}P. An aliquot of purified nGPCR-x (*ca.* 15 µg) or crude nGPCR-x extract (*ca.* 15 ng) is incubated at constant temperature (in the range 22-37 C) for at least 30 minutes in 10-15 µl of buffer (*i.e.* TAE or TBE, pH 8.0-8.5) containing radiolabeled probe DNA, nonspecific carrier DNA (*ca.* 1 µg), BSA (300 µg/ml), and 10% (v/v) glycerol. The reaction mixture is then loaded onto a polyacrylamide gel and run at 30-35 mA until good separation of free probe DNA from protein-DNA complexes occurs. The gel is then dried and bands corresponding to free DNA and protein-DNA complexes are detected by autoradiography.

EXAMPLE 10: ANTIBODIES TO nGPCR-X

Standard techniques are employed to generate polyclonal or monoclonal antibodies to the nGPCR-x receptor, and to generate useful antigen-binding fragments thereof or variants thereof, including "humanized" variants. Such protocols can be found, for example, in Sambrook *et al.* (1989) and Harlow *et al.* (Eds.), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988). In one embodiment, recombinant nGPCR-x polypeptides (or cells or cell membranes containing such polypeptides) are used as antigen to generate the antibodies. In another embodiment, one or more peptides having amino acid sequences corresponding to an immunogenic portion of nGPCR-x (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,or more amino acids) are used as antigen. Peptides corresponding to extracellular portions of nGPCR-x, especially hydrophilic extracellular portions, are preferred. The antigen may be mixed with an adjuvant or linked to a hapten to increase antibody production.

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A. Polyclonal or Monoclonal antibodies

As one exemplary protocol, recombinant nGPCR-x or a synthetic fragment thereof is used to immunize a mouse for generation of monoclonal antibodies (or larger mammal, such as a rabbit, for polyclonal antibodies). To increase antigenicity, peptides are conjugated to Keyhole Lympet Hemocyanin (Pierce), according to the manufacturer's recommendations. For an initial injection, the antigen is emulsified with Freund's Complete Adjuvant and injected subcutaneously. At intervals of two to three weeks, additional aliquots of nGPCR-x antigen are emulsified with Freund's Incomplete Adjuvant and injected subcutaneously. Prior to the final booster injection, a serum sample is taken from the immunized mice and assayed by western blot to confirm the presence of antibodies that immunoreact with nGPCR-x. Serum from the immunized animals may be used as polyclonal antisera or used to isolate polyclonal antibodies that recognize nGPCR-x. Alternatively, the mice are sacrificed and their spleen removed for generation of monoclonal antibodies.

To generate monoclonal antibodies, the spleens are placed in 10 ml serum-free RPMI 1640, and single cell suspensions are formed by grinding the spleens in serum-free RPMI 1640, supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, and 100 µg/ml streptomycin (RPMI) (Gibco, Canada). The cell suspensions are filtered and washed by centrifugation and resuspended in serum-free RPMI. Thymocytes taken from three naive Balb/c mice are prepared in a similar manner and used as a Feeder Layer. NS-1 myeloma cells, kept in log phase in RPMI with 10% fetal bovine serum (FBS) (Hyclone Laboratories, Inc., Logan, Utah) for three days prior to fusion, are centrifuged and washed as well.

To produce hybridoma fusions, spleen cells from the immunized mice are combined with NS-1 cells and centrifuged, and the supernatant is aspirated. The cell pellet is dislodged by tapping the tube, and 2 ml of 37°C PEG 1500 (50% in 75 mM HEPES, pH 8.0) (Boehringer-Mannheim) is stirred into the pellet, followed by the addition of serum-free RPMI. Thereafter, the cells are centrifuged, resuspended in RPMI containing 15% FBS, 100 µM sodium hypoxanthine, 0.4 µM aminopterin, 16 µM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer-Mannheim) and 1.5 x 10^6

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thymocytes/ml, and plated into 10 Corning flat-bottom 96-well tissue culture plates (Corning, Corning New York).

On days 2, 4, and 6 after the fusion, 100µl of medium is removed from the wells of the fusion plates and replaced with fresh medium. On day 8, the fusions are screened by ELISA, testing for the presence of mouse IgG that binds to nGPCR-x. Selected fusion wells are further cloned by dilution until monoclonal cultures producing anti-nGPCR-x antibodies are obtained.

B. Humanization of anti-nGPCR-x monoclonal antibodies

The expression pattern of nGPCR-x as reported herein and the proven track record of GPCRs as targets for therapeutic intervention suggest therapeutic indications for nGPCR-x inhibitors (antagonists). nGPCR-x-neutralizing antibodies comprise one class of therapeutics useful as nGPCR-x antagonists. Following are protocols to improve the utility of anti-nGPCR-x monoclonal antibodies as therapeutics in humans by "humanizing" the monoclonal antibodies to improve their serum half-life and render them less immunogenic in human hosts (*i.e.*, to prevent human antibody response to non-human anti-nGPCR-x antibodies).

The principles of humanization have been described in the literature and are facilitated by the modular arrangement of antibody proteins. To minimize the possibility of binding complement, a humanized antibody of the IgG4 isotype is preferred.

For example, a level of humanization is achieved by generating chimeric antibodies comprising the variable domains of non-human antibody proteins of interest with the constant domains of human antibody molecules. (See, *e.g.*, Morrison *et al.*, Adv. Immunol., 44:65-92 (1989)). The variable domains of nGPCR-x-neutralizing anti-nGPCR-x antibodies are cloned from the genomic DNA of a B-cell hybridoma or from cDNA generated from mRNA isolated from the hybridoma of interest. The V region gene fragments are linked to exons encoding human antibody constant domains, and the resultant construct is expressed in suitable mammalian host cells (*e.g*, myeloma or CHO cells).

To achieve an even greater level of humanization, only those portions of the variable region gene fragments that encode antigen-binding complementarity determining regions ("CDR") of the non-human monoclonal antibody genes are cloned into human

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antibody sequences. (See, *e.g.*, Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature 332:323-327 (1988); Verhoeyen *et al.*, Science 239:1534-36 (1988); and Tempest *et al.*, Bio/Technology 9: 266-71 (1991)). If necessary, the β-sheet framework of the human antibody surrounding the CDR3 regions also is modified to more closely mirror the three dimensional structure of the antigen-binding domain of the original monoclonal antibody. (See Kettleborough *et al.*, Protein Engin., 4:773-783 (1991); and Foote *et al.*, J. Mol. Biol., 224:487-499 (1992)).

In an alternative approach, the surface of a non-human monoclonal antibody of interest is humanized by altering selected surface residues of the non-human antibody, *e.g.*, by site-directed mutagenesis, while retaining all of the interior and contacting residues of the non-human antibody. See Padlan, Molecular Immunol., 28(4/5):489-98 (1991).

The foregoing approaches are employed using nGPCR-x-neutralizing anti-nGPCR-x monoclonal antibodies and the hybridomas that produce them to generate humanized nGPCR-x-neutralizing antibodies useful as therapeutics to treat or palliate conditions wherein nGPCR-x expression or ligand-mediated nGPCR-x signaling is detrimental.

C. Human nGPCR-x-Neutralizing Antibodies from Phage Display

Human nGPCR-x-neutralizing antibodies are generated by phage display techniques such as those described in Aujame *et al.*, Human Antibodies 8(4):155-168 (1997); Hoogenboom, TIBTECH 15:62-70 (1997); and Rader *et al.*, Curr. Opin. Biotechnol. 8:503-508 (1997), all of which are incorporated by reference. For example, antibody variable regions in the form of Fab fragments or linked single chain Fv fragments are fused to the amino terminus of filamentous phage minor coat protein pIII. Expression of the fusion protein and incorporation thereof into the mature phage coat results in phage particles that present an antibody on their surface and contain the genetic material encoding the antibody. A phage library comprising such constructs is expressed in bacteria, and the library is screened for nGPCR-x-specific phage-antibodies using labeled or immobilized nGPCR-x as antigen-probe.

D. Human nGPCR-x-neutralizing antibodies from transgenic mice

Human nGPCR-x-neutralizing antibodies are generated in transgenic mice essentially as described in Bruggemann *et al.*, Immunol. Today 17(8):391-97 (1996) and

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Bruggemann *et al.*, Curr. Opin. Biotechnol. 8:455-58 (1997). Transgenic mice carrying human V-gene segments in germline configuration and that express these transgenes in their lymphoid tissue are immunized with a nGPCR-x composition using conventional immunization protocols. Hybridomas are generated using B cells from the immunized mice using conventional protocols and screened to identify hybridomas secreting anti-nGPCR-x human antibodies (*e.g.*, as described above).

EXAMPLE 11: ASSAYS TO IDENTIFY MODULATORS OF nGPCR-X ACTIVITY

Set forth below are several nonlimiting assays for identifying modulators (agonists and antagonists) of nGPCR-x activity. Among the modulators that can be identified by these assays are natural ligand compounds of the receptor; synthetic analogs and derivatives of natural ligands; antibodies, antibody fragments, and/or antibody-like compounds derived from natural antibodies or from antibody-like combinatorial libraries; and/or synthetic compounds identified by high-throughput screening of libraries; and the like. All modulators that bind nGPCR-x are useful for identifying nGPCR-x in tissue samples (*e.g.*, for diagnostic purposes, pathological purposes, and the like). Agonist and antagonist modulators are useful for up-regulating and down-regulating nGPCR-x activity, respectively, to treat disease states characterized by abnormal levels of nGPCR-x activity. The assays may be performed using single putative modulators, and/or may be performed using a known agonist in combination with candidate antagonists (or visa versa).

A. cAMP Assays

In one type of assay, levels of cyclic adenosine monophosphate (cAMP) are measured in nGPCR-x-transfected cells that have been exposed to candidate modulator compounds. Protocols for cAMP assays have been described in the literature. (See,*e.g.*, Sutherland *et al.*, Circulation 37: 279 (1968); Frandsen *et al.*, Life Sciences 18: 529-541 (1976); Dooley *et al.*, Journal of Pharmacology and Experimental Therapeutics 283 (2): 735-41 (1997); and George *et al.*, Journal of Biomolecular Screening 2 (4): 235-40 (1997)). An exemplary protocol for such an assay, using an Adenylyl Cyclase Activation FlashPlate® Assay from NEN™ Life Science Products, is set forth below.

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Briefly, the nGPCR-x coding sequence (*e.g.*, a cDNA or intronless genomic DNA) is subcloned into a commercial expression vector, such as pzeoSV2 (Invitrogen), and transiently transfected into Chinese Hamster Ovary (CHO) cells using known methods, such as the transfection protocol provided by Boehringer-Mannheim when supplying the FuGENE 6 transfection reagent. Transfected CHO cells are seeded into 96-well microplates from the FlashPlate® assay kit, which are coated with solid scintillant to which antisera to cAMP has been bound. For a control, some wells are seeded with wild type (untransfected) CHO cells. Other wells in the plate receive various amounts of a cAMP standard solution for use in creating a standard curve.

One or more test compounds (*i.e.*, candidate modulators) are added to the cells in each well, with water and/or compound-free medium/diluent serving as a control or controls. After treatment, cAMP is allowed to accumulate in the cells for exactly 15 minutes at room temperature. The assay is terminated by the addition of lysis buffer containing [^{125}I]-labeled cAMP, and the plate is counted using a Packard Topcount™ 96-well microplate scintillation counter. Unlabeled cAMP from the lysed cells (or from standards) and fixed amounts of [^{125}I]-cAMP compete for antibody bound to the plate. A standard curve is constructed, and cAMP values for the unknowns are obtained by interpolation. Changes in intracellular cAMP levels of cells in response to exposure to a test compound are indicative of nGPCR-x modulating activity. Modulators that act as agonists of receptors which couple to the G_s subtype of G proteins will stimulate production of cAMP, leading to a measurable 3-10 fold increase in cAMP levels. Agonists of receptors which couple to the $G_{i/o}$ subtype of G proteins will inhibit forskolin-stimulated cAMP production, leading to a measurable decrease in cAMP levels of 50-100%. Modulators that act as inverse agonists will reverse these effects at receptors that are either constitutively active or activated by known agonists.

B. Aequorin Assays

In another assay, cells (*e.g.*, CHO cells) are transiently co-transfected with both a nGPCR-x expression construct and a construct that encodes the photoprotein apoaquorin. In the presence of the cofactor coelenterazine, apoaquorin will emit a measurable luminescence that is proportional to the amount of intracellular (cytoplasmic) free calcium. (See generally, Cobbold, *et al.* "Aequorin measurements of cytoplasmic free

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calcium," *In*: McCormack J.G. and Cobbold P.H., eds., *Cellular Calcium: A Practical Approach*. Oxford:IRL Press (1991); Stables *et al.*, Analytical Biochemistry 252: 115-26 (1997); and Haugland, Handbook of Fluorescent Probes and Research Chemicals. Sixth edition. Eugene OR: Molecular Probes (1996).)

In one exemplary assay, nGPCR-x is subcloned into the commercial expression vector pzeoSV2 (Invitrogen) and transiently co-transfected along with a construct that encodes the photoprotein apoaquorin (Molecular Probes, Eugene, OR) into CHO cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert.

The cells are cultured for 24 hours at 37°C in MEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin, at which time the medium is changed to serum-free MEM containing 5 µM coelenterazine (Molecular Probes, Eugene, OR). Culturing is then continued for two additional hours at 37°C. Subsequently, cells are detached from the plate using VERSEN (Gibco/BRL), washed, and resuspended at 200,000 cells/ml in serum-free MEM.

Dilutions of candidate nGPCR-x modulator compounds are prepared in serum-free MEM and dispensed into wells of an opaque 96-well assay plate at 50 µl/well. Plates are then loaded onto an MLX microtiter plate luminometer (Dynex Technologies, Inc., Chantilly, VA). The instrument is programmed to dispense 50µl cell suspensions into each well, one well at a time, and immediately read luminescence for 15 seconds. Dose-response curves for the candidate modulators are constructed using the area under the curve for each light signal peak. Data are analyzed with SlideWrite, using the equation for a one-site ligand, and EC_{50} values are obtained. Changes in luminescence caused by the compounds are considered indicative of modulatory activity. Modulators that act as agonists at receptors which couple to the G_q subtype of G proteins give an increase in luminescence of up to 100 fold. Modulators that act as inverse agonists will reverse this effect at receptors that are either constitutively active or activated by known agonists.

C. Luciferase Reporter Gene Assay

The photoprotein luciferase provides another useful tool for assaying for modulators of nGPCR-x activity. Cells (*e.g.*, CHO cells or COS 7 cells) are transiently

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co-transfected with both a nGPCR-x expression construct (*e.g.*, nGPCR-x in pzeoSV2) and a reporter construct which includes a gene for the luciferase protein downstream from a transcription factor binding site, such as the cAMP-response element (CRE), AP-1, or NF-kappa B. Agonist binding to receptors coupled to the G_s subtype of G proteins leads to increases in cAMP, thereby activating the CRE transcription factor and resulting in expression of the luciferase gene. Agonist binding to receptors coupled to the G_q subtype of G protein leads to production of diacylglycerol that activates protein kinase C, which activates the AP-1 or NF-kappa B transcription factors, in turn resulting in expression of the luciferase gene. Expression levels of luciferase reflect the activation status of the signaling events. (See generally, George *et al.*, Journal of Biomolecular Screening 2(4): 235-240 (1997); and Stratowa *et al.*, Current Opinion in Biotechnology 6: 574-581 (1995)). Luciferase activity may be quantitatively measured using, *e.g.*, luciferase assay reagents that are commercially available from Promega (Madison, WI).

In one exemplary assay, CHO cells are plated in 24-well culture dishes at a density of 100,000 cells/well one day prior to transfection and cultured at 37°C in MEM (Gibco/BRL) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin. Cells are transiently co-transfected with both a nGPCR-x expression construct and a reporter construct containing the luciferase gene. The reporter plasmids CRE-luciferase, AP-1-luciferase and NF-kappaB-luciferase may be purchased from Stratagene (LaJolla, CA). Transfections are performed using the FuGENE 6 transfection reagent (Boehringer-Mannheim) according to the supplier's instructions. Cells transfected with the reporter construct alone are used as a control. Twenty-four hours after transfection, cells are washed once with PBS pre-warmed to 37°C. Serum-free MEM is then added to the cells either alone (control) or with one or more candidate modulators and the cells are incubated at 37°C for five hours. Thereafter, cells are washed once with ice-cold PBS and lysed by the addition of 100 µl of lysis buffer per well from the luciferase assay kit supplied by Promega. After incubation for 15 minutes at room temperature, 15 µl of the lysate is mixed with 50 µl of substrate solution (Promega) in an opaque-white, 96-well plate, and the luminescence is read immediately on a Wallace model 1450 MicroBeta scintillation and luminescence counter (Wallace Instruments, Gaithersburg, MD).

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Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity. Receptors that are either constitutively active or activated by agonists typically give a 3 to 20-fold stimulation of luminescence compared to cells transfected with the reporter gene alone. Modulators that act as inverse agonists will reverse this effect.

D. Intracellular calcium measurement using FLIPR

Changes in intracellular calcium levels are another recognized indicator of G protein-coupled receptor activity, and such assays can be employed to screen for modulators of nGPCR-x activity. For example, CHO cells stably transfected with a nGPCR-x expression vector are plated at a density of 4 x 10^4 cells/well in Packard black-walled, 96-well plates specially designed to discriminate fluorescence signals emanating from the various wells on the plate. The cells are incubated for 60 minutes at 37°C in modified Dulbecco's PBS (D-PBS) containing 36 mg/L pyruvate and 1 g/L glucose with the addition of 1% fetal bovine serum and one of four calcium indicator dyes (Fluo-3™ AM, Fluo-4™ AM, Calcium Green™-1 AM, or Oregon Green™ 488 BAPTA-1 AM), each at a concentration of 4 μM. Plates are washed once with modified D-PBS without 1% fetal bovine serum and incubated for 10 minutes at 37°C to remove residual dye from the cellular membrane. In addition, a series of washes with modified D-PBS without 1% fetal bovine serum is performed immediately prior to activation of the calcium response.

A calcium response is initiated by the addition of one or more candidate receptor agonist compounds, calcium ionophore A23187 (10 μM; positive control), or ATP (4 μM; positive control). Fluorescence is measured by Molecular Device's FLIPR with an argon laser (excitation at 488 nm). (See, *e.g.*, Kuntzweiler *et al.*, Drug Development Research, 44(1):14-20 (1998)). The F-stop for the detector camera was set at 2.5 and the length of exposure was 0.4 milliseconds. Basal fluorescence of cells was measured for 20 seconds prior to addition of candidate agonist, ATP, or A23187, and the basal fluorescence level was subtracted from the response signal. The calcium signal is measured for approximately 200 seconds, taking readings every two seconds. Calcium ionophore A23187 and ATP increase the calcium signal 200% above baseline levels. In general, activated GPCRs increase the calcium signal approximately 10-15% above baseline signal.

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E. Mitogenesis Assay

In a mitogenesis assay, the ability of candidate modulators to induce or inhibit nGPCR-x-mediated cell division is determined. (*See, e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3): 1573-1581 (1993)). For example, CHO cells stably expressing nGPCR-x are seeded into 96-well plates at a density of 5000 cells/well and grown at 37°C in MEM with 10% fetal calf serum for 48 hours, at which time the cells are rinsed twice with serum-free MEM. After rinsing, 80µl of fresh MEM, or MEM containing a known mitogen, is added along with 20µl MEM containing varying concentrations of one or more candidate modulators or test compounds diluted in serum-free medium. As controls, some wells on each plate receive serum-free medium alone, and some receive medium containing 10% fetal bovine serum. Untransfected cells or cells transfected with vector alone also may serve as controls.

After culture for 16-18 hours, 1µ Ci of [^{3}H]-thymidine (2 Ci/mmol) is added to the wells and cells are incubated for an additional 2 hours at 37°C. The cells are trypsinized and collected on filter mats with a cell harvester (Tomtec); the filters are then counted in a Betaplate counter. The incorporation of [^{3}H]-thymidine in serum-free test wells is compared to the results achieved in cells stimulated with serum (positive control). Use of multiple concentrations of test compounds permits creation and analysis of dose-response curves using the non-linear, least squares fit equation: $A = B \times [C/(D + C)] + G$ where A is the percent of serum stimulation; B is the maximal effect minus baseline; C is the EC_{50}; D is the concentration of the compound; and G is the maximal effect. Parameters B,C and G are determined by Simplex optimization.

Agonists that bind to the receptor are expected to increase [^{3}H]-thymidine incorporation into cells, showing up to 80% of the response to serum. Antagonists that bind to the receptor will inhibit the stimulation seen with a known agonist by up to 100%.

F. [^{35}S]GTPγS Binding Assay

Because G protein-coupled receptors signal through intracellular G proteins whose activity involves GTP binding and hydrolysis to yield bound GDP, measurement of binding of the non-hydrolyzable GTP analog [^{35}S]GTPγS in the presence and absence of candidate modulators provides another assay for modulator activity. (*See, e.g.*, Kowal *et al.*, Neuropharmacology 37:179-187 (1998).)

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In one exemplary assay, cells stably transfected with a nGPCR-x expression vector are grown in 10 cm tissue culture dishes to subconfluence, rinsed once with 5 ml of ice-cold Ca^{2+}/Mg^{2+}-free phosphate-buffered saline, and scraped into 5 ml of the same buffer. Cells are pelleted by centrifugation (500 x *g*, 5 minutes), resuspended in TEE buffer (25 mM Tris, pH 7.5, 5 mM EDTA, 5 mM EGTA), and frozen in liquid nitrogen. After thawing, the cells are homogenized using a Dounce homogenizer (one ml TEE per plate of cells), and centrifuged at 1,000 x *g* for 5 minutes to remove nuclei and unbroken cells.

The homogenate supernatant is centrifuged at 20,000 x *g* for 20 minutes to isolate the membrane fraction, and the membrane pellet is washed once with TEE and resuspended in binding buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA). The resuspended membranes can be frozen in liquid nitrogen and stored at -70°C until use.

Aliquots of cell membranes prepared as described above and stored at -70°C are thawed, homogenized, and diluted into buffer containing 20 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA, 120 mM NaCl, 10 µM GDP, and 0.2 mM ascorbate, at a concentration of 10-50 µg/ml. In a final volume of 90 µl, homogenates are incubated with varying concentrations of candidate modulator compounds or 100 µM GTP for 30 minutes at 30°C and then placed on ice. To each sample, 10 µl guanosine 5'-O-(3[^{35}S]thio) triphosphate (NEN, 1200 Ci/mmol; [^{35}S]-GTPγS), was added to a final concentration of 100-200 pM. Samples are incubated at 30°C for an additional 30 minutes, 1 ml of 10mM HEPES, pH 7.4, 10 mM $MgCl_2$, at 4°C is added and the reaction is stopped by filtration.

Samples are filtered over Whatman GF/B filters and the filters are washed with 20 ml ice-cold 10 mM HEPES, pH 7.4, 10 mM $MgCl_2$. Filters are counted by liquid scintillation spectroscopy. Nonspecific binding of [^{35}S]-GTPγS is measured in the presence of 100 µM GTP and subtracted from the total. Compounds are selected that modulate the amount of [^{35}S]-GTPγS binding in the cells, compared to untransfected control cells. Activation of receptors by agonists gives up to a five-fold increase in [^{35}S]GTPγS binding. This response is blocked by antagonists.

G. MAP Kinase Activity Assay

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Evaluation of MAP kinase activity in cells expressing a GPCR provides another assay to identify modulators of GPCR activity. (See, *e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3):1573-1581 (1993) and Boulton *et al.*, Cell 65:663-675 (1991).)

In one embodiment, CHO cells stably transfected with nGPCR-x are seeded into 6-well plates at a density of 70,000 cells/well 48 hours prior to the assay. During this 48-hour period, the cells are cultured at 37°C in MEM medium supplemented with 10% fetal bovine serum, 2mM glutamine, 10 U/ml penicillin and 10μg/ml streptomycin. The cells are serum-starved for 1-2 hours prior to the addition of stimulants.

For the assay, the cells are treated with medium alone or medium containing either a candidate agonist or 200 nM Phorbol ester- myristoyl acetate (*i.e.*, PMA, a positive control), and the cells are incubated at 37°C for varying times. To stop the reaction, the plates are placed on ice, the medium is aspirated, and the cells are rinsed with 1 ml of ice-cold PBS containing 1mM EDTA. Thereafter, 200μl of cell lysis buffer (12.5 mM MOPS, pH 7.3, 12.5 mM glycerophosphate, 7.5mM $MgCl_2$, 0.5mM EGTA, 0.5 mM sodium vanadate, 1mM benzamidine, 1mM dithiothreitol, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 2μg/ml pepstatin A, and 1μM okadaic acid) is added to the cells. The cells are scraped from the plates and homogenized by 10 passages through a 23 3/4 G needle, and the cytosol fraction is prepared by centrifugation at 20,000 x *g* for 15 minutes.

Aliquots (5-10 μl containing 1-5 μg protein) of cytosol are mixed with 1 mM MAPK Substrate Peptide (APRTPGGRR (SEQ ID NO: 241), Upstate Biotechnology, Inc., N.Y.) and 50μM [γ-^{32}P]ATP (NEN, 3000 Ci/mmol), diluted to a final specific activity of ~2000 cpm/pmol, in a total volume of 25 μl. The samples are incubated for 5 minutes at 30°C, and reactions are stopped by spotting 20 μl on 2 cm^2 squares of Whatman P81 phosphocellulose paper. The filter squares are washed in 4 changes of 1% H_3PO_4, and the squares are subjected to liquid scintillation spectroscopy to quantitate bound label. Equivalent cytosolic extracts are incubated without MAPK substrate peptide, and the bound label from these samples are subtracted from the matched samples with the substrate peptide. The cytosolic extract from each well is used as a separate point. Protein concentrations are determined by a dye binding protein assay (Bio-Rad Laboratories).

Agonist activation of the receptor is expected to result in up to a five-fold increase in MAPK enzyme activity. This increase is blocked by antagonists.

H. [^{3}H]Arachidonic Acid Release

The activation of GPCRs also has been observed to potentiate arachidonic acid release in cells, providing yet another useful assay for modulators of GPCR activity. (*See, e.g.*, Kanterman *et al.*, Molecular Pharmacology 39:364-369 (1991).) For example, CHO cells that are stably transfected with a nGPCR-x expression vector are plated in 24-well plates at a density of 15,000 cells/well and grown in MEM medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin for 48 hours at 37°C before use. Cells of each well are labeled by incubation with [^{3}H]-arachidonic acid (Amersham Corp., 210 Ci/mmol) at 0.5 µCi/ml in 1 ml MEM supplemented with 10mM HEPES, pH 7.5, and 0.5% fatty-acid-free bovine serum albumin for 2 hours at 37°C. The cells are then washed twice with 1 ml of the same buffer.

Candidate modulator compounds are added in 1 ml of the same buffer, either alone or with 10µM ATP and the cells are incubated at 37°C for 30 minutes. Buffer alone and mock-transfected cells are used as controls. Samples (0.5 ml) from each well are counted by liquid scintillation spectroscopy. Agonists which activate the receptor will lead to potentiation of the ATP-stimulated release of [^{3}H]-arachidonic acid. This potentiation is blocked by antagonists.

I. Extracellular Acidification Rate

In yet another assay, the effects of candidate modulators of nGPCR-x activity are assayed by monitoring extracellular changes in pH induced by the test compounds. (*See, e.g.*, Dunlop *et al.*, Journal of Pharmacological and Toxicological Methods 40(1):47-55 (1998).) In one embodiment, CHO cells transfected with a nGPCR-x expression vector are seeded into 12 mm capsule cups (Molecular Devices Corp.) at 4 x 10^5 cells/cup in MEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 U/ml penicillin, and 10 µg/ml streptomycin. The cells are incubated in this medium at 37°C in 5% CO_2 for 24 hours.

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Extracellular acidification rates are measured using a Cytosensor microphysiometer (Molecular Devices Corp.). The capsule cups are loaded into the sensor chambers of the microphysiometer and the chambers are perfused with running buffer (bicarbonate-free MEM supplemented with 4 mM L-glutamine, 10 units/ml penicillin, 10 µg/ml streptomycin, 26 mM NaCl) at a flow rate of 100 µl/minute. Candidate agonists or other agents are diluted into the running buffer and perfused through a second fluid path. During each 60-second pump cycle, the pump is run for 38 seconds and is off for the remaining 22 seconds. The pH of the running buffer in the sensor chamber is recorded during the cycle from 43-58 seconds, and the pump is re-started at 60 seconds to start the next cycle. The rate of acidification of the running buffer during the recording time is calculated by the Cytosoft program. Changes in the rate of acidification are calculated by subtracting the baseline value (the average of 4 rate measurements immediately before addition of a modulator candidate) from the highest rate measurement obtained after addition of a modulator candidate. The selected instrument detects 61mV/pH unit. Modulators that act as agonists of the receptor result in an increase in the rate of extracellular acidification compared to the rate in the absence of agonist. This response is blocked by modulators which act as antagonists of the receptor.

Example 12 - Using nGPCR-x proteins to isolate neurotransmitters

Isolated nGPCR-x proteins of the present invention can be used to isolate novel or known neurotransmitters (Saito *et al.*, Nature 400: 265-269, 1999). The cDNAs that encode the isolated nGPCR-x can be cloned into mammalian expression vectors and used to stably or transiently transfect mammalian cells including CHO, Cos or HEK293 cells. Receptor expression can be determined by Northern blot analysis of transfected cells and identification of an appropriately sized mRNA band (predicted size from the cDNA). Brain regions shown by mRNA analysis to express each of the nGPCR-x proteins could be processed for peptide extraction using any of several protocols ((Reinsheidk R.K. *et al.*, Science 270: 243-247, 1996; Sakurai, T., *et al.*, Cell 92: 573-585, 1998; Hinuma, S., *et al.*, Nature 393: 272-276, 1998). Chromotographic fractions of brain extracts could be tested

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for ability to activate nGPCR-x proteins by measuring second messenger production such as changes in cAMP production in the presence or absence of forskolin, changes in inositol 3-phosphate levels, changes in intracellular calcium levels or by indirect measures of receptor activation including receptor stimulated mitogenesis, receptor mediated changes in extracellular acidification or receptor mediated changes in reporter gene activation in response to cAMP or calcium (these methods should all be referenced in other sections of the patent). Receptor activation could also be monitored by co-transfecting cells with a chimeric $GI_{q/i3}$ to force receptor coupling to a calcium stimulating pathway (Conklin *et al.*, Nature 363; 274-276, 1993). Neurotransmitter mediated activation of receptors could also be monitored by measuring changes in [^{35} S]-GTPKS binding in membrane fractions prepared from transfected mammalian cells. This assay could also be performed using baculoviruses containing nGPCR-x proteins infected into SF9 insect cells.

The neurotransmitter which activates nGPCR-x proteins can be purified to homogeneity through successive rounds of purification using nGPCR-x proteins activation as a measurement of neurotransmitter activity. The composition of the neurotransmitter can be determined by mass spectrometry and Edman degradation if peptidergic. Neurotransmitters isolated in this manner will be bioactive materials which will alter neurotransmission in the central nervous system and will produce behavioral and biochemical changes.

Example 13 - Using nGPCR-x proteins to isolate and purify G proteins

cDNAs encoding nGPCR-x proteins are epitope–tagged at the amino terminuus end of the cDNA with the cleavable influenza-hemagglutinin signal sequence followed by the FLAG epitope (IBI, New Haven, CT). Additionally, these sequences are tagged at the carboxyl terminus with DNA encoding six histidine residues. (Amino and Carboxyl Terminal Modifications to Facilitate the Production and Purification of a G Protein-Coupled Receptor, B.K. Kobilka , *Analytical Biochemistry*, Vol. 231, No. 1, Oct 1995, pp. 269-271). The resulting sequences are cloned into a baculovirus expression vector such as pVL1392 (Invitrogen). The baculovirus expression vectors are used to infect SF-9 insect cells as described (Guan, X. M., Kobilka, T. S., and Kobilka, B. K. (1992)*J. Biol. Chem.*

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267, 21995-21998). Infected SF-9 cells could be grown in 1000-ml cultures in SF900 II medium (Life Technologies, Inc.) containing 5% fetal calf serum (Gemini, Calabasas, CA) and 0.1 mg/ml gentamicin (Life Technologies, Inc.) for 48 hours at which time the cells could be harvested. Cell membrane preparations could be separated from soluble proteins following cell lysis. nGPCR-x protein purification is carried out as described for purification of the 92 receptor (Kobilka, Anal. Biochem., 231 (1): 269-271, 1995) including solubilization of the membranes in 0.8-1.0 % *n*-dodecyl -*D*-maltoside (*DM*) (CalBiochem, La Jolla, CA) in buffer containing protease inhibitors followed by Ni-column chromatography using chelating Sepharose™ (Pharmacia, Uppsala, Sweden). The eluate from the Ni-column is further purified on an M1 anti-FLAG antibody column (IBI). Receptor containing fractions are monitored by using receptor specific antibodies following western blot analysis or by SDS-PAGE analysis to look for an appropriate sized protein band (appropriate size would be the predicted molecular weight of the protein).

This method of purifying G protein is particularly useful to isolate G proteins that bind to the nGPCR-x proteins in the absence of an activating ligand.

Some of the preferred embodiments of the invention described above are outlined below and include, but are not limited to, the following embodiments. As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

The entire disclosure of each publication cited herein is hereby incorporated by reference.

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What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of: SEQ ID NO:121 to SEQ ID NO:240; said nucleic acid molecule encoding at least a portion of nGPCR-x.

2. The isolated nucleic acid molecule of claim 1 comprising a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240.

3. The isolated nucleic acid molecule of claim 1 comprising a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120.

4. The isolated nucleic acid molecule of claim 1 comprising a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120.

5. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is DNA.

6. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is RNA.

7. An expression vector comprising a nucleic acid molecule of any one of claims 1 to 4.

8. The expression vector of claim 7 wherein said nucleic acid molecule comprises a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120.

9. The expression vector of claim 7 wherein said vector is a plasmid.

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10. The expression vector of claim 7 wherein said vector is a viral particle.

11. The expression vector of claim 10 wherein said vector is selected from the group consisting of adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses.

12. The expression vector of claim 7 wherein said nucleic acid molecule is operably connected to a promoter selected from the group consisting of simian virus 40, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein.

13. A host cell transformed with an expression vector of claim 7.

14. The transformed host cell of claim 13 wherein said cell is a bacterial cell.

15. The transformed host cell of claim 14 wherein said bacterial cell is E. coli.

16. The transformed host cell of claim 13 wherein said cell is yeast.

17. The transformed host cell of claim 16 wherein said yeast is S. cerevisiae.

18. The transformed host cell of claim 13 wherein said cell is an insect cell.

19. The transformed host cell of claim 18 wherein said insect cell is S. frugiperda.

20. The transformed host cell of claim 13 wherein said cell is a mammalian cell.

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21. The transformed host cell of claim 20 wherein mammalian cell is selected from the group consisting of chinese hamster ovary cells, HeLa cells, African green monkey kidney cells, human HEK-293 cells, and murine 3T3 fibroblasts.

22. An isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120, said portion comprising at least 10 nucleotides.

23. The nucleic acid molecule of claim 22 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120.

24. The nucleic acid molecule of claim 23 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120.

25. A composition comprising a nucleic acid molecule of any one of claims 1 to 4 or 22 and an acceptable carrier or diluent.

26. A composition comprising a recombinant expression vector of claim 7 and an acceptable carrier or diluent.

27. A method of producing a polypeptide that comprises a sequence selected from the group of sequences consisting SEQ ID NO:121 to SEQ ID NO:240, and homologs thereof, said method comprising the steps of:

a) introducing a recombinant expression vector of claim 8 into a compatible host cell;

b) growing said host cell under conditions for expression of said polypeptide; and

c) recovering said polypeptide.

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28. The method of claim 27 wherein said host cell is lysed and said polypeptide is recovered from the lysate of said host cell.

29. The method of claim 27 wherein said polypeptide is recovered by purifying the culture medium without lysing said host cell.

30. An isolated polypeptide encoded by a nucleic acid molecule of claim 1.

31. The polypeptide of claim 30 wherein said polypeptide comprises a sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

32. The polypeptide of claim 30 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

33. The polypeptide of claim 30 wherein said sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240 comprises at least one conservative amino acid substitution compared to the sequences in the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

34. The polypeptide of claim 30 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

35. A composition comprising a polypeptide of claim 34 and an acceptable carrier or diluent.

36. An isolated antibody which binds to an epitope on a polypeptide of claim 30.

37. The antibody of claim 36 wherein said antibody is a monoclonal antibody.

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38. A composition comprising an antibody of claim 36 and an acceptable carrier or diluent.

39. A method of inducing an immune response in a mammal against a polypeptide of claim 30 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.

40. A method for identifying a compound which binds nGPCR-x comprising the steps of:

a) contacting nGPCR-x with a compound; and

b) determining whether said compound binds nGPCR-x.

41. The method of claim 40 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:SEQ ID NO:121 to SEQ ID NO:240.

42. The method of claim 40 wherein binding of said compound to nGPCR-x is determined by a protein binding assay.

43. The method of claim 40 wherein said protein binding assay is selected from the group consisting of a gel-shift assay, Western blot, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, and ELISA.

44. A compound identified by the method of claim 40.

45. A method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x comprising the steps of:

a) contacting said nucleic acid molecule encoding nGPCR-x with a compound; and

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b) determining whether said compound binds said nucleic acid molecule.

46. The method of claim 45 wherein binding is determined by a gel-shift assay.

47. A compound identified by the method of claim 45.

48. A method for identifying a compound which modulates the activity of nGPCR-x comprising the steps of:

a) contacting nGPCR-x with a compound; and

b) determining whether nGPCR-x activity has been modulated.

49. The method of claim 48 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240.

50. The method of claim 48 wherein said activity is neuropeptide binding.

51. The method of claim 48 wherein said activity is neuropeptide signaling.

52. A compound identified by the method of claim 48.

53. A method of identifying an animal homolog of nGPCR-x comprising the steps:

a) comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequence consisting of SEQ ID NO:1 to SEQ ID NO:120, and portions thereof, said portions being at least 10 nucleotides; and

b) identifying nucleic acid sequences of the animal that are homologous to said sequence selected from the group sequence consisting of SEQ ID NO:1 to SEQ ID NO:120, and portions thereof, said portions comprising at least 10 nucleotides.

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54. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120, and portions thereof, said portions being at least 10 nucleotides, is performed by DNA hybridization.

55. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:120, and portions thereof, said portions being at least 10 nucleotides, is performed by computer homology search.

56. A method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and allelic variants thereof, and wherein the nucleic acid corresponds to a gene encoding the nGPCR-x; and

(b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

57. A method according to claim 56, wherein the disease is a mental disorder.

58. A method according to claim 56, wherein the assaying step comprises at least one procedure selected from the group consisting of:

a) comparing nucleotide sequences from the human subject and reference sequences and determining a difference of at least a nucleotide of at least one codon between the nucleotide sequences from the human subject that encodes a nGPCR-x reference sequence;

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(b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences;

(c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and

(d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

59. A method according to claim 58 wherein the assaying step comprises: performing a polymerase chain reaction assay to amplify nucleic acid comprising nGPCR-x coding sequence, and determining nucleotide sequence of the amplified nucleic acid.

60. A method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from said patient, said nucleic acid including sequences corresponding to alleles of nGPCR-x; and

(b) detecting the presence of one or more mutations in the nGPCR-x allele;

wherein the presence of a mutation in a nGPCR-x allele is indicative of a hereditary mental disorder genotype.

61. The method according to claim 60 wherein said biological sample is a cell sample.

62. The method according to claim 60 wherein said detecting the presence of a mutation comprises sequencing at least a portion of said nucleic acid, said portion comprising at least one codon of said nGPCR-x allele, said portion comprising at least 10 nucleotides.

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63. The method according to claim 60 wherein said nucleic acid is DNA.

64. The method according to claim 60 wherein said nucleic acid is RNA.

65. A kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association:

(a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene, the oligonucleotide comprising 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and

(b) a media packaged with the oligonucleotide, said media containing information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

66. A method of identifying a nGPCR-x allelic variant that correlates with a mental disorder, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny;

(b) detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:121 to SEQ ID NO:240, and allelic variants thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding nGPCR-x;

wherein the one or more mutations detected indicates an allelic variant that correlates with a mental disorder.

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67. A purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x allelic variant identified according to claim 66.

68. A host cell transformed or transfected with a polynucleotide according to claim 67 or with a vector comprising the polynucleotide.

69. A purified polynucleotide comprising a nucleotide sequence encoding nGPCR-x of a human with a mental disorder;

wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and

(b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and

wherein the polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from the sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 by at least one residue.

70. A vector comprising a polynucleotide according to claim 69.

71. A host cell that has been transformed or transfected with a polynucleotide according to claim 69 and that expresses the nGPCR-x protein encoded by the polynucleotide.

72. A host cell according to claim 71 that has been co-transfected with a polynucleotide encoding the nGPCR-x amino acid sequence set forth in a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:120 and that expresses the nGPCR-x protein having the amino acid sequence set forth in SEQ ID NO:121 to SEQ ID NO:240.

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73. A method for identifying a modulator of biological activity of nGPCR-x comprising the steps of:

a) contacting a cell according to claim 72 in the presence and in the absence of a putative modulator compound;

b) measuring nGPCR-x biological activity in the cell;

wherein decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

74. A method to identify compounds useful for the treatment of a mental disorder, said method comprising the steps of:

(a) contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x;

(b) detecting binding between nGPCR-x and the compound suspected of binding nGPCR-x;

wherein compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of a mental disorder.

75. A method for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x comprising the steps of:

(a) contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound;

(b) detecting binding between the binding partner and nGPCR-x;

wherein decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a mental disorder.

76. A method according to claim 74 or 75 wherein the composition comprises a cell expressing nGPCR-x on its surface.

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77. A method according to claim 76 wherein the composition comprises a cell transformed or transfected with a polynucleotide that encodes nGPCR-x.

78. A method of purifying a G protein from a sample containing said G protein comprising the steps of:

a) contacting said sample with a polypeptide of claim 1 for a time sufficient to allow said G protein to form a complex with said polypeptide;

b) isolating said complex from remaining components of said sample;

c) maintaining said complex under conditions which result in dissociation of said G protein from said polypeptide; and

d) isolating said G protein from said polypeptide.

79. The method of claim 78 wherein said sample comprises an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

80. The method of claim 78 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:121 to SEQ ID NO:240.

81. The method of claim 78 wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:121 to SEQ ID NO:240.

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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ttaatcacca agacaatggg gaaaatgtct ccagggcatg gcagagacct ttacagcagc 480

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<211> 569
<212> DNA
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ataagcataa attctactaa agttgaaaga catggaatat tcatataaat ggagtacatt 180

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<210> 46
<211> 654
<212> DNA
<213> Homo sapiens

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ccctggaaga aataataaga aaaataaaat aataaattat aataatagcc aacctttgtt 600

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cctgcagaga ttattctaca cacagg 626

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<211> 606
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<212> DNA
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<400> 49
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<213> Homo sapiens

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<211> 642
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

<400> 53
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tggcagaagg cagcctttct gttaaatctg ggaatttatc agaaagagga caacccaagc 420

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<211> 573
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<212> DNA
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ggtggaccct gcccagtcaa agca 624

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<212> DNA
<213> Homo sapiens

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gattgaacat actaacaatt taaaggaaat ctttgtcctt cagaaaaagc acacaaggag 180

tattacaagg tgtttgccag tcttcaaacc aaggcaaagc aagaaccaca gatgcctcct 240

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<211> 515
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<213> Homo sapiens

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<211> 473
<212> DNA
<213> Homo sapiens

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<212> DNA
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<212> DNA
<213> Homo sapiens

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ggtgatgttt gggatgcatc ttgaaagagg gacaaaagtt tgccaggaga agtggggtga 480

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<210> 83
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<212> DNA
<213> Homo sapiens

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<210> 84
<211> 459
<212> DNA
<213> Homo sapiens

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ttcatatttt tcctgtaagt cttaaccttt tagttaaatt accacaagta ttttaaaatt 480

tttatattaa aaatcaaaga tcagtctgaa aataataaca tttttctttt aatttctcat 540

<210> 86
<211> 653
<212> DNA
<213> Homo sapiens

<400> 86
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aaccagagac agaaaccccc aaagatctaa actctctgta gagagcatgc agtgacagtt 180

tagcctatgc tacctgaagt ggaaatagat cattctttaa ataaatcact tgtgctgact 240

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aagaaactct gtatgacaca gttttcaagt gcacacctat tcaaaattgc aagtgatatc 480

tcttttgtac tgatttagcc tgtacctgaa agcaatagcc atacacatga gtatactgaa 540

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<211> 594
<212> DNA
<213> Homo sapiens

<400> 87
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<210> 88
<211> 530
<212> DNA
<213> Homo sapiens

<400> 88
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gctacaaagt tatacttact tagaattagt atttcatctt gaaactagct cccaatataa 180

ctacagcata aggagacatt ttattagaaa tttaaatttc aaggtaagaa attatctcat 240

tgaaaattgt catattattt tactcaaatt acgtatagaa actcatacaa ttataattac 300

aaaagttcca acttccagtt accgaaattt actatgagct caacaaaaca tcaccaaaaa 360

gtatccatac attaaaaaaa aaacctattt catacagaat tatactgttt tagccaatta 420

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aaatacatgt gttcaattca acaagttcct acatccattc gccttgcact 530

<210> 89
<211> 347
<212> DNA
<213> Homo sapiens

<400> 89
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gcgcagagat ataaggggtt ggggtacttg cccctccccc agaaaagtgg tacttgcccg 300

ctaagggtga aggagaaagg ggttgggggt ttcttgcacc ccagaaa 347

<210> 90
<211> 523
<212> DNA
<213> Homo sapiens

<400> 90
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gtgttaaaat tggagtcaag gcactttagg tcttcttaca tggagttaag aaaatttaaa 420

gcaatttttgt aaatgaagaa tttcacaatg catgtctatt attgctcttt cattcccaat 480

ctaatcattg ttaaagtgtt ctaagtttct tctacagtag tcg 523

<210> 91
<211> 714
<212> DNA
<213> Homo sapiens

<400> 91
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tactttggcc aacatgaatt ggttacatgt gccttaaaat tttttaaatt atatttctag 180

gaaaaatcaa tcatcactta caaattgttt tacaatctaa gaactataca tttctctaag 240

taaaattata aatcccaggc atgtaactat tcacatcaaa ttttgttttt cagacaaagg 300

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aaaggtaaga agccatctat actttcccgt tccatccaat acatttttgt tactatttta 420

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ttttaatatt aaatatctgc aattctattc tagctcctgt gacaaaattc aagaaaacct 540

gacataaatg aacaacaata caacatgtat tcaaccatct atgatctctt ccatggcttt 600

accaatcatt tacatcctcc tttgtattgg tggtgttttt ggaaacactc tctctcaatg 660

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<210> 92
<211> 474
<212> DNA
<213> Homo sapiens

<400> 92
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tctctgtgac agttccatta cctcaaatct aaaataaggt cactcctgta cagtgctgtc 180

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atagatcggc atacaaaagt aatagtactg aagataccac atctctatcc tcatctgaaa 420

cagaaggaaa tcaaatgtgc accaaggctt actgaattgc tacaatgttg gaga 474

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<211> 503
<212> DNA
<213> Homo sapiens

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tgttactcat ttattcattc actcatcaaa aggcaccatg aaagaaaatc agagtgcaat 240

gatggatgga caagccagac tttttatcta caaccttaga atgtaaagtt agctaggaag 300

acagtcacag aaaatataat taaaggtcta tgaatattat gaagaggaat tacagaatgc 360

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aaatagttta ggcaggaaga ataagtaggt gttggcaaga aagggatcca ggatattcca 480

ggcacatgaa acacagatgc aga 503

<210> 94
<211> 511
<212> DNA
<213> Homo sapiens

<400> 94
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tatttaaata atctaaaact atggcccata ggccaaagct agctcactgc ctgtttttgt 480

atagcttaca aaatggtttt tacatttttt t 511

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<211> 632
<212> DNA
<213> Homo sapiens

<400> 95
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agcatagtag gctgtcttag ctgagcacaa actgatattc agtttgttat tggtgaaaca 180

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caaaaacttg gatgcaataa agaataaatg taagaggttc cacactagaa ggtggggaag 540

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<211> 660
<212> DNA
<213> Homo sapiens

<400> 96
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<211> 376
<212> DNA
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<400> 97
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<211> 660
<212> DNA
<213> Homo sapiens

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<400> 100
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tttgctgtgt gtccaactcc tctgatgagg tcagaatgtc tgatttccca cacccaagga 540

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<210> 101
<211> 525
<212> DNA
<213> Homo sapiens

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<211> 658
<212> DNA
<213> Homo sapiens

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<211> 579
<212> DNA
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aaaggtgtcc agcagagaaa agagcatata caaagccctg tgctaagaat gagcttggca 540

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<210> 104
<211> 369

<212> DNA
<213> Homo sapiens

<400> 104
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tagagtttga ttatgtcatg ctaatttaat gaaaatgaat tagttttaaa gagttttaaa 180

cataagggaa aatgtgtaac taatatgaaa tcctgtatgt ttatttgctt cactatggta 240

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<210> 105
<211> 220
<212> DNA
<213> Homo sapiens

<400> 105
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actgtacatt atattttgtt tgtagaaata gaataggatt aaactggtac aattacaaag 120

taatttgtcc aatgaggaaa agacacctaa gtctacagtg cacttggaga cctaggcatg 180

atgaaaagga aggaacagga cagtttttt cttgccaact 220

<210> 106
<211> 624
<212> DNA
<213> Homo sapiens

<400> 106
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ttttttcttca ttcattcctt cactggctta ggctataaac ctaccagtca tccctagttc 120

ttttcttcct gtaactacta atcatttccc tcttcgttcc cctgagctga atcatcactc 180

cagccacttc caatttaaca gtacattctt taaaacatac agtgatctca tagtttgtct 240

tcatctctgt ggaatcacat ctatatctaa cctggattat cacaatagcc tccaaactga 300

ctttgctgtt tccaagacat ttgcctccct gctgtatatt ttctgcccag gagctgtaat 360

aacattttaa aaatataaat catatcaggt cacttccctg cttaaaactt tgcaatggtc 420

tcagtaaact taaaaaatat ccaaagttct taaaacggct tacattattt agatttttct 480

tttccaactc atttcccaat ctttttcttt tgacactatt gccttctctt tacatccttg 540

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tataatctac cactaccaga tact 624

<210> 107
<211> 511

ENSDOCID <WO 0166751A2_I_>

<212> DNA
<213> Homo sapiens

<400> 107
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atgagtggtc tgattccatc tggctctgct gctcaaatgg cagttgggat gatagtcatg 120

ctacagacac atttaccaac taagcagtgc agacagtact ctgcattggc ccaaatttac 180

ctaggaacaa gcacaggtgt gctcagataa ggaaaatacc ttaggtcagg agggggggtg 240

agcacatggt tggtaaaata gaatttagtg agttaaaaaa aaaaccagca aaccaacaca 300

agactcataa gtaccctata gtatctgcgg atgccgttac acgtcaagtt aaaccacatc 360

ttctcaggat acaggggtgt tttgcagctc tcacattaac acagatgtgt aacgtgggtt 420

tctcagccta tcagaaatgg ggcaagatag ggttataata aacagctttt gtttttttg 480

gctctgccct tactagggga gacttccaac c 511

<210> 108
<211> 643
<212> DNA
<213> Homo sapiens

<400> 108
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taaacactag catttagaaa atgtacaata aatgatagca gctcagttca ttataattat 120

catagcctta aagaaatagt agaaagaaga aaaacactga acttgggcca agctgtgctg 180

aaagctcatc tctgctactt gtgagttgtg tgattttggg tgatttataa tcttcgaggg 240

ctttttttt ctttgtctgt aaaatggcgt tagtttcacc taatatctac aagttattag 300

gaaaattaaa tgatatgcta atctaaaaac ttgccattca atgaatgtta attaattttc 360

tctttgaaga tgctggtggt taggtgctct agtattctct attttttct actgtttttc 420

cccctctact gtgctgttac tcatttattc attcactcat caaaaggcac catgaaagaa 480

aatcagagtg caatgatgga tggacaagcc agactttta tctacaacct tagaatgtaa 540

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gaattacaga atgctttgaa agcttataaa tgagaaccta atc 643

<210> 109
<211> 481
<212> DNA
<213> Homo sapiens

<400> 109
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catgttatca gagacatcat tgcaaattgc cagttgttct gcaaccacac aactttgttt 120

cttctttctc cagtttctat cactcttttt gcttttggt cacttacagg attttttcc 180

ccccaagtcc aagtgttcca aaatatcaca tttacactct tcttattgcc tttccagcca 240

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atgtaagagc ttcacattat cataattgat atatatgtga gctagaataa ttttttttta 420

aatcagtttt cccttgaaca tctcaggcag cagcgttcag tggaatgtga ctgtgtcgga 480

a 481

<210> 110
<211> 575
<212> DNA
<213> Homo sapiens

<400> 110
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cccaacccca atttgcaaaa gataggagag gtatgcttgt gtgtgtacgt gtgtgtgtgt 120

gtgtgtgtgt gtgtgtgtgt gtgtgttggt gttgtttttt agctcctggc attcaaggaa 180

atctctgtca aaacactggc taaacacaag ctgaagaaac agacactttg gtgaccacaa 240

aaaaacaatg aatagtcttt gcaaaaatag cttgggaaag tataaaaaca aacattacta 300

cagtcttcag aaattaaaaa aaaatgctga ggaagagaga gaatctgatt tccagactta 360

tcacattata atagtcaaat gtccagtttt caacagcaac agcaaaatca caagtcagac 420

aaatgggaaa agatggccta ttcaaaggaa aaaaaaaaac aagttgaaaa aactgtgtcc 480

aaggcagccc aacattacac ttattagaca aaaaacttta aaatagctat cttaaagagc 540

taagagcaaa aatggatgag gactaaagta aatta 575

<210> 111
<211> 356
<212> DNA
<213> Homo sapiens

<400> 111
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gcgctctcgc gtttcacgca gcggccgggg atctgggaca ggcggggccc cgaggccgag 120

cctggctgct gcccagcggc cggtgcaggc ctcaagctgg gccgggcgga ggggaaccgg 180

cgagttgaag ccccggggcc gaaagccgga gcctgtggcg gccgcggggg tggggagggg 240

ggtggggcgg cttcttgggc agcgccacac ggcggcgcag tgatggatgt taacagcagc 300

tggccacccg gacctctacg ggcgcctctg ctctttcctc ctgccggagg tggggg 356

<210> 112
<211> 607
<212> DNA
<213> Homo sapiens

<400> 112
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BNSDOCID <WO 0166751A2_I_>

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ttctgagatc aaccttgcag agtgtgcctt ggtgtcatcc tcatcttaca ggtgtggaag 240

ctgaggccta atgaggccat gtgtcttccg ttccccttat acaccatggg acatggggca 300

gagcataagc ttgaaccccg gtctctaggt ttttttctac cacacagtgc agtgagagac 360

atgaaggggg ttgatgtgta tggaatacat atacatgcac atccagctat acttttaaaa 420

aaaatattat tggatgggtc tgggttctct attttataag tgacacatac aactattgaa 480

cccatgtgag attatagcca ggagtgcata aaaaactgtc ctcagaacaa gttgaatggg 540

aagttgggta aaaacgaata aggttgagtt cactccacag ccccacagat gcaactgatt 600

taattga 607

<210> 113
<211> 579
<212> DNA
<213> Homo sapiens

<400> 113
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aaccccaacc ctccctgctt ctgtgcccag gctcctgcca gagtcagaag atggcagtgg 120

tcactgggtg gagacaaaga cagccaagga accatcccag gtaggcaaga aggcaacagg 180

aggtgggacc aggagggaga tgaggcttca agtttccaag tcttccttgt cccatcagac 240

ttcacttaca aaatacgaat tcaaagacag ctactgaaag ttgcaggaca atgaccatga 300

gcattaaact ccaagtgtgg ggcccgtttg agtaccagct acactgatga cacacccatg 360

tgcttcttta gtagtaaaat aggaaatgag gcttctccaa ttctctcccc tccctgcaca 420

caggatttta actctgatga agtccagttt atctattttt ggaagtgtga ttctcccacg 480

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gagagactta cctaatccca tggctgggag ccacacaat 579

<210> 114
<211> 673
<212> DNA
<213> Homo sapiens

<400> 114
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tcattcaaaa atttaaataa atgtctatta tctatcctgt tccattcttg aaaattatga 180

taactcaaga ggtaggtatc tcagggaaag aacactgtga tgtgtggctg gagcaagaaa 240

tgtgtatctc ttgttcagtg ttgagttttg gctcgtagaa tagagactgg ctcataatag 300

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tagtcataaa ctgcctgagc agtatgtggg aaagtgctgg cccaggagat agctggatat 420

ctgggagcct tttcatccca ggaggctctt cctgggggcc ttcccactca gccatgggaa 480

gctgcttctc tctctatgaa gtttagactt tcctgtgcac ccagaggtat ctttcaacaa 540

tcaggagctg agtgcttaga caaagggtga ggtgagcttg gacaaaaatc aagatgaata 600

tctgtgacta tgcacatact tggtacagac acgtccatat atgccacaga cacaaataca 660

tggagattga act 673

<210> 115
<211> 628
<212> DNA
<213> Homo sapiens

<400> 115
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ctccccgtgg tgctccaagc tcagtgggtg gcagcacagc acgatggttc aggacagtgt 120

ctctggaggg tgctctgggc ccgtcactaa ccagctgggc ggccccaagt gagtcacata 180

acctctctgt ctgcctcatt atctgtaaaa agaggatgtg gtagcatttg cctaacagca 240

aatgtaactg ataattaatg catataaaat gcttagaata gtgaaaaatg gtgttcaaag 300

aagcattcgt tgttattgtt gtgtttctat ggggtgaggt agccagtaaa acccaaggtt 360

aacaccagac tgtttttcctc taggaaatac aacaaacaag caagcagaag acatggatcc 420

tgaagtttct tatgagcagg agactagcac agaccactgt tcctaccatt gggaggacag 480

cacacctggc tggctgccag agtgggcctt ggggagtagg aaaagccaag ggcttaagag 540

atggaagatc tcctgggtca cacccaggag actattcact agctgcccac tggacaataa 600

acaccaactg aggacccagg tgacacaa 628

<210> 116
<211> 584
<212> DNA
<213> Homo sapiens

<400> 116
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tttcccaagg atggccccaa tagctcccat cccacatgct cttgaccctg ccatgctgca 180

tcaggagatg gagtctaatt gccctctcct tgaatttgtg ctgtcttgat gacctacttg 240

ttaatgactg aataaaatga aagtgttgct gcttgagttt cgagacaaag tcagtaaagg 300

ccatgaagcc tctacctggt tctcatgcaa cattcactcc aggggaagtc aactgccatg 360

taataagttt aataattctg agaccactat ggtaaagagg ccacagataa ttgctccttt 420

aggtagtccc agctgatccc agctttcatc catccttcca agacatcaga cacgtcagtg 480

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ctacagggag ccagagagtc acccagccaa gtcctgcctg ccta 584

<210> 117
<211> 674
<212> DNA
<213> Homo sapiens

<400> 117
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tgaaacaaca taaagcatct tgcaactctg gctaattttt ttctcctcct tatactcaca 180

aaagctttct agttgacggt atttcttctg tccttggcac gtgacaaaga cttgaggcca 240

aagtctgcat gtgatgtcag cctccgtgaa agactcatat ctcttctgct ctccatcaat 300

aggggagggg gcacagaggt atctggggag tgtctggcgt ttagcatctt tgtacagagc 360

cagtctcagt ggatgtagcc tcaggactgt gcagagaaaa tcacctggct tattcagaag 420

ggcattaagg acagcagtgg aaaccaatgg tgcctacata agtcagattc tccctcttgt 480

aactccagaa taggaccaaa tctcccctca ctcactcaaa gcccaaacaa tagttcatgg 540

agaaaagaac aaccaactct tacacaattg ggaaaaaaca ggttctctat gcacacaaga 600

gactattaag cagaagccac attagactgt ccatttcctc tttgcaccag ggaagtgagt 660

agggcagtct gcag 674

<210> 118
<211> 635
<212> DNA
<213> Homo sapiens

<400> 118
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tgcttaacaa gcaaaatggc atcagaaaga gggtgaacaa ataaaggtat atttagggct 120

aatgatgaat tcgaggtaaa gcacatcaat gtttccacca aggtttttgc ttccagtgtg 180

gtagggcaaa aagatgtgaa ctgaattatt ggtactctca aattaaatgt attcatttta 240

ttaattcatt tagcaacaga catacacagg tacatatacc catatccgta gtttcactta 300

taaagaaaaa ttaaatccac ccaactgttt tgttttctgc aatattttta acttctgtga 360

ctttttgttt tttccattgc tttgaatcca caataggtag gtaggagaat ttgaagcacc 420

attgaaatga agtattctag aaaagtatgc agaaagataa agaaaatgca tccatctcta 480

gaagtgctta catctactta gcaagtgtga aactcacaat gaggatttag cctgttagta 540

tggcacagat tataaatagg agagtcgctg ttataatgta atataattaa cacaattgtt 600

cttgttatag agcatgatag tagctaccac ctgtc 635

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<210> 119
<211> 663
<212> DNA
<213> Homo sapiens

<400> 119
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attaattgtt tattgattaa atatttaaca gaattggatc atcatttggt ctctggccca 120

gcatatcagt ggtaggagtt aatcaaaagg atcatttgcc ccagaagagt ggctttcaaa 180

tttagcatgc attggaatcc ccctggaggg cttgttaaca cagattattg aactctaccc 240

cgagagtttc tggttcagta ggtcttgggt tggcttgaga atttgcattt ctagcaaact 300

ttcaggtgat gctgatgctg ctggtccagg gaccacgctt tgagtgagaa ccacgggacg 360

agagaaacca ctgaagagca gagattcatt ttgaagacta caccatagga aggaggcaga 420

aagtagaaag aagcactcca ctgcataaag ctgaaactgg catccaggaa tgagagatac 480

caggcaagct ttggatgatt acaggaaata acttctcaaa ggtaaaaaat gaagtcagat 540

ctccttacac ctatagtagc ttttttaaag ttcccatttc atcaagaatc aagacaagga 600

tcataaagga aattgtcttt gaggctgcat gccctacctg attgctcttg aactggaact 660

cag 663

<210> 120
<211> 561
<212> DNA
<213> Homo sapiens

<400> 120
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ttttttattt ctttctttga cttcttcact tccatgattt ctctttggtt tctttacatc 120

tatctctttg tggaatttct cattcaaatc ctgatttgtt ttccttattt ctttgtgtag 180

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acagtattat aggccccata ggatttctcc tgctgtaaac agtgtgagtg gtgtctgtga 540

gctcctcagt ggcttaacaa c 561

<210> 121
<211> 159
<212> PRT
<213> Homo sapiens

<400> 121

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Leu Asn Ile Ile Phe Phe Ser Thr Ser Glu Asn Lys Glu Leu Val Phe
1               5                  10                  15

Asn Pro Leu Pro Cys Pro Ile Ile Phe Pro Val Val Pro Phe Trp Leu
            20                  25                  30

Gly Leu Lys Leu Phe Gln Cys Lys His His Val Ile Thr Ser Phe His
        35                  40                  45

Ala Gln His Phe Val Leu Pro Gly Ile Asp Asn Cys Leu Val Phe Ala
    50                  55                  60

Phe Ser Val Ser Phe Leu Ile Phe Ser Gln Thr Ile Leu Leu Gly Val
65                  70                  75                  80

Leu His Pro Gly Val Cys Ile Leu Leu Arg Gly Asp Glu Gly Lys Ala
                85                  90                  95

Glu Phe Leu Asn Ile Gln Tyr Ile Asn Phe His Ile Ile Ser Ile Cys
            100                 105                 110

His Tyr Gly Thr Ser Ala Leu Thr Met Arg Arg Met Ser Ser Arg Asp
        115                 120                 125

Leu Leu Leu Pro Thr Lys Asp Thr Pro Ser Trp Leu Pro Gly Trp Gly
    130                 135                 140

Gly Val Ala Pro Ser Cys Arg Val Arg Glu Arg Ile Pro Lys Ile
145                 150                 155

<210>  122
<211>  203
<212>  PRT
<213>  Homo sapiens

<400>  122

Leu Pro Gln Pro Leu Thr Leu Ser Ser Asn Pro Ser Ser Arg Pro Ile
1               5                  10                  15

Lys Ser Glu Ser Leu Glu Met Gly Ile Trp His Gln Tyr Phe Lys Leu
            20                  25                  30

Ser Val Leu Lys Asn Tyr Phe Phe Asn Glu Lys Asn Ile Thr Ser Tyr
        35                  40                  45

Phe Asn Ile Trp Val His Cys Gly Met Ala Asn Leu Arg Val Thr Tyr
    50                  55                  60

Gln Leu Pro His Thr Leu Ile Ile Phe Leu Cys Pro Gly Thr Phe Lys
65                  70                  75                  80

Thr Gln Ser Gly Asn His Gly Val Ile Pro Asp Thr Ser Leu Ser Leu
                85                  90                  95

Cys Pro Gln Ala Gln Leu Ile His Gln Gln Asp Met Trp Met Gly Cys
            100                 105                 110

Phe Phe Ser Lys Cys Leu Glu Phe Ile His Phe Phe His Cys Cys His
        115                 120                 125

Asn His Pro Pro Gly Pro Gly Ala Ile Phe Ser Cys Leu Glu Asn Cys
    130                 135                 140
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Asn Ser Pro Glu Phe Val His Ile His Met Thr Pro Ser Leu Leu Cys
145 150 155 160

Thr Leu Phe Leu Asn Pro Val Val Ile Phe Phe Thr Ala Glu Ile Ser
165 170 175

Tyr Gln Ala Pro Ser Leu Arg His Phe Cys Thr Phe Pro Thr Asp Ser
180 185 190

Ser His Cys Leu Gln Arg Pro Ala Pro Thr Arg
195 200

<210> 123
<211> 229
<212> PRT
<213> Homo sapiens

<400> 123

Ser Val Ser Pro Leu Gln Gly Gly Gly Gln Ala Gly Arg Arg Val Gly
1 5 10 15

Glu Gly Val Ile Ala Tyr Met Ala Ala Gly Thr Glu Ala Arg Asn Arg
20 25 30

Arg Ala Glu Gly Glu Gly Ser Asp Arg Thr Glu Gly Cys Arg Ile Ala
35 40 45

Gly Arg Cys Pro Glu Leu Cys Glu Phe Gly Ala Gln Pro Gln Arg Arg
50 55 60

Phe Arg Arg Val Pro Val Leu Ala Leu Ala Arg Gly Ala Arg Thr Val
65 70 75 80

Phe Leu Arg Phe Leu Arg Pro Lys Arg Val Ser Pro Phe Phe Pro Leu
85 90 95

Gly Met Pro Lys Ala Thr Gly Lys Asp Arg Lys Leu Ser Pro Arg Arg
100 105 110

Ile Leu Ser Lys Met Arg Pro Ser Arg Gln Arg His Leu Ser Arg Ala
115 120 125

Pro Ala Pro Arg Cys Pro Ser Arg Gly Gly Thr Gly Gly Glu Val Ala
130 135 140

Gly Ala Leu Pro Arg Glu Tyr Pro Gly Ser Gln Thr Thr Arg His Arg
145 150 155 160

Pro Arg Leu Ala Pro Leu Leu Leu Leu Pro His Ser Arg Cys Leu Leu
165 170 175

Phe Arg Leu Pro Leu Lys Arg Pro Pro Ser Ala Gly Val Leu Arg Thr
180 185 190

Pro Ser Thr Ala Met Ala His Ser Asn Thr Phe Thr Gly Cys Leu Phe
195 200 205

Ala His Leu Lys Lys Trp Ile Ile Ser Arg Leu Pro Ala Tyr Arg Thr
210 215 220

Cys Arg Gly Gln Arg
225

<210> 124

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<211> 145
<212> PRT
<213> Homo sapiens

<400> 124

Ser Leu Phe Asn Ser Ser Phe Tyr His Lys Gly Met Asn Tyr Arg Ala
1 5 10 15

Val Ile Glu Lys Tyr Asp Asn Val Cys Ala Ser Arg Arg Arg Leu Ser
20 25 30

Phe His Leu Lys Asn Lys Phe Gln Ile Arg Arg Ser Gln Ile Val Thr
35 40 45

Phe Trp Ile Tyr Asp Arg Tyr Leu Leu Cys His Leu Asn Asp Thr Lys
50 55 60

Asn Thr Val Cys Ala Val Leu Cys Val Pro Leu Tyr Arg Thr Cys Met
65 70 75 80

Phe Ser Asn Leu Tyr Thr Cys Ile Leu Cys Phe Ile Val Leu Tyr Cys
85 90 95

Thr Ser Gln Ile Leu Gln Arg Phe Glu Gly Leu Gln Pro Cys Ile Asp
100 105 110

Gln Ile Cys Trp Pro Asn Phe Ser Asn Ser Ile Phe Ser Phe Tyr Val
115 120 125

Thr Tyr Leu Leu Gln Tyr Phe Lys Val Phe Ile Ile Ile Leu Ser Gly
130 135 140

Met
145

<210> 125
<211> 204
<212> PRT
<213> Homo sapiens

<400> 125

Val Ser His Ser Ala Lys Asn Val Leu Lys Leu Pro Gln Pro Tyr Gln
1 5 10 15

Leu Asp Tyr Leu Ser Glu Ser Ile Ile Asn Asn Leu Trp Ser His Ile
20 25 30

Lys Val Ile Lys Asn Leu Ile Ser Pro Arg Tyr Arg Thr Ile Ser Cys
35 40 45

Ser Gln Ala Phe Asn Phe Ile Pro Asn Met Pro Ile Val Glu Phe Cys
50 55 60

Leu Asn Met Tyr Phe Phe Ile Met Gln Met Lys Val Cys Asp Phe Thr
65 70 75 80

Thr Thr Lys Ile Ser Val Ile Leu Phe Ile Val Phe Val Ser Phe Asn
85 90 95

Ile Leu Tyr Tyr Asp Pro Arg Leu Pro Val Ser Ile Trp Ile Lys Gly
100 105 110

Asp Ser Ser Ser Trp Ile Ser Lys Phe Thr Arg Thr Asp Phe Trp Leu

ENSDOCID <WO 0166751A2_I_>

115 120 125

Phe Asp Ala Lys Arg Gly Arg Val Arg His Pro Ser Trp Gln Pro Asn
130 135 140

Gly Ser Glu Leu Glu Ala Leu Gly Lys Ala Gly Arg Arg Pro Gln Pro
145 150 155 160

Cys Arg Lys Cys Leu Ser Leu Val Pro His Gln Pro Pro Cys His Gly
165 170 175

Ala Leu Gln Lys Pro Asp Leu Lys Ser Val His Ala Gly Leu Asp Val
180 185 190

Lys Tyr Asn Thr Ser His Phe Thr Pro Cys Trp Pro
195 200

<210> 126
<211> 195
<212> PRT
<213> Homo sapiens

<400> 126

Leu Phe Ser Ser Val Pro Phe Cys Leu Ser Glu Tyr Leu Pro Ile Leu
1 5 10 15

Val Cys Asn Arg Leu Ile Ile Tyr Met Trp Leu Lys Met Ser Pro Leu
20 25 30

Asp Lys Val Lys Phe Cys Phe Leu Thr Asn Ile Pro Pro Ser Tyr Ser
35 40 45

Leu Lys Val Thr Thr Ala Thr Leu Ile Tyr Leu Phe Leu Arg Tyr Gln
50 55 60

Thr Ala Ile Thr Glu His Cys Ala Ser Cys Val Leu His Ile Thr Arg
65 70 75 80

Cys Thr Leu Lys Ile Ile Phe Ile Lys Leu Leu Phe Arg Ser Lys Ile
85 90 95

His Ser Leu Cys Thr Val Leu Gln Val Leu Lys Ser Ala Tyr Ser Cys
100 105 110

Val Ser Ile Thr Lys Ile Lys Pro Tyr Asn Ser Cys Ile Thr Pro Lys
115 120 125

Arg Gly Ile Leu Cys Pro Phe Ala Ile Ser Leu Phe Ser Thr Pro Gln
130 135 140

Pro Trp Gln Thr Ile Cys Phe Leu Thr Leu Gln Phe Leu Val Phe Ile
145 150 155 160

Leu His Phe His Phe Asn Ser Val Leu Cys Ile Phe Tyr Phe Pro Gly
165 170 175

Phe Leu Ile Asp Ser Ile Asn Ile Cys Val Phe Pro Ser Ser Trp Arg
180 185 190

Leu Phe Leu
195

<210> 127
<211> 178

ENSDOCID <WO 0166751A2 I >

<212> PRT
<213> Homo sapiens

<400> 127

Phe Pro Met Thr Leu Gln Tyr Gly Cys Lys Cys Phe Met Ile Glu Ile
1 5 10 15

Leu Tyr Tyr Lys Phe Gln Ser Tyr Leu Lys Gly Ser Ser Leu Val Gly
20 25 30

Cys Thr Gln Glu Asn Ser Thr Ala Ser Gln Gly Leu Ser Asn Val Ser
35 40 45

Cys Pro Gln Lys Arg Asp Leu Phe Leu Lys Gly Lys Phe Ile Phe Lys
50 55 60

Asn Gln Gln Ala Asn Gln Pro Arg Gln Ile Leu Asn Pro Ser Pro Asp
65 70 75 80

Arg Glu Ala Gly Lys Arg Ile Leu Lys Cys Thr Ile Lys Arg Trp Leu
85 90 95

Tyr Met Trp Lys Asn Thr Asn Phe His Asn Lys His Ser Ile Ile Asn
100 105 110

Ala Asn Arg Lys Tyr Ile Tyr Cys Leu Pro Gln Pro Ile Val Tyr Leu
115 120 125

Leu Gly Glu Pro Cys His Cys Ala Phe Arg Arg Gln Trp Trp Arg Val
130 135 140

Cys Leu Thr His Thr Phe Thr Thr Asp Pro Arg Trp Leu Pro Cys Ser
145 150 155 160

Phe Val Arg Asn Lys Gly Ile Arg Phe Val Pro Ser Trp Ala Ile Lys
165 170 175

Asn Leu

<210> 128
<211> 176
<212> PRT
<213> Homo sapiens

<400> 128

Pro Pro Trp Cys Gln Gly Lys Pro Ala Pro His Ser Asn Leu Thr Ile
1 5 10 15

Ile Gln Ala Leu Phe Gln Leu Leu Ala Trp Leu Lys Ser Gly Pro Ser
20 25 30

Ala Ala Glu Pro Arg Glu Gly Cys Arg Gly Leu Gly Thr Gly Phe Ala
35 40 45

Trp Pro Gly Gly Tyr Glu Arg Leu Gln Pro Ala Arg Ala Thr Leu Cys
50 55 60

Gln Ser Ser Ile Ser Val Leu Lys Ala Pro Thr Cys Leu Asp Arg Val
65 70 75 80

Gly Gly Val Asn Asp Gly Met Gln Ser Pro Gln Ser Tyr Thr His Ala
85 90 95

Gln Leu Ala His Ala Pro Cys Leu Lys Pro Trp Leu Pro Ala His His
100 105 110

Leu Glu Gln Glu Gly Gln Val Pro Tyr Gly Leu Gln Pro Leu Trp Pro
115 120 125

Trp Ala Pro Pro Ser Val Ile Pro Leu His Ser Leu Phe Pro Leu Val
130 135 140

Val Val Ala Cys Leu Cys Val Phe Ile Asn Val Phe Ser Leu Cys Arg
145 150 155 160

Ala Ala Ser Cys Leu Phe Phe Gln Ile Trp Leu Leu Leu Ser Leu Pro
165 170 175

<210> 129
<211> 128
<212> PRT
<213> Homo sapiens

<400> 129

Phe Leu Phe Glu Lys Leu Met Thr Met Asp Pro Val Leu Cys Gly Leu
1 5 10 15

Tyr Phe Ser Phe Ser Gly Gln Ser Arg Lys Lys Tyr Thr Thr Ala Glu
20 25 30

Lys Gly Ile Thr Leu Arg Lys Lys His Lys Tyr Phe Gly His Lys Arg
35 40 45

Ala Phe Leu Leu Ser Lys Cys Pro Ile Arg Phe Phe Ala Thr Val Ile
50 55 60

Phe Asn His Gln Val Gln Cys Leu Lys Gly Cys Phe Ser Asn Ser Phe
65 70 75 80

Gly Val Cys Gln Thr Gly Met Gln Val Leu Ile Cys Gln Ser Ile Ala
85 90 95

Val Pro Tyr Thr Ser Tyr Leu Ala Thr Leu Ser His Lys Ser Phe Ile
100 105 110

Trp Lys Thr Val Ser His Leu Thr Glu Leu Leu Pro Leu Lys Tyr Ala
115 120 125

<210> 130
<211> 178
<212> PRT
<213> Homo sapiens

<400> 130

Phe Leu Gln Ala Arg Lys Trp Thr Leu Thr Lys Ile Phe Leu Thr Leu
1 5 10 15

Ile Leu Ala Ser Gln Pro Pro Glu Leu Gln Ile Asn Ile Cys Cys Ser
20 25 30

Ser Tyr Pro Val Met Val Phe Cys Tyr Ser Ser Ser Ile Gln Ala Gln
35 40 45

Ile Asn Ile Cys Cys Ser Ser Tyr Pro Val Met Val Phe Cys Tyr Ser
50 55 60

BNSDOCID <WO 0166751A2 >

```
Ser Ser Ile Arg Gly His Lys His Ser Ser Ser Ser His Thr Asp Ile
65                  70                  75                  80

Glu Leu Gln Thr Thr Gly Ile Ile Lys Asn Val His Cys Ala Phe Asn
                85                  90                  95

Arg Val Tyr Trp Gly Pro Leu Gly Gln Tyr Met Arg Leu Leu Leu Arg
            100                 105                 110

Tyr Asp Lys Leu Ser Pro Glu Gly Leu Val Thr Val Asn Gln Val Lys
        115                 120                 125

Asp Glu Val Ala Phe Gln Asp Gly Glu Ser Glu Cys Thr Glu Val Leu
    130                 135                 140

Asn Gln Glu Gly Glu Thr His Gln Leu Thr Glu Arg Lys Ala Lys Pro
145                 150                 155                 160

Arg Asn Leu Asn Met Ser Arg Glu Glu Trp Gly Met Val Val Gly Trp
                165                 170                 175

Glu Trp
```

<210> 131
<211> 208
<212> PRT
<213> Homo sapiens

<400> 131

```
Thr Cys Thr Ser Thr Arg Arg Lys Ile Leu Leu Leu Phe Phe Ile Phe
1               5                   10                  15

Ser Ser Thr Ser Pro Val Pro Ser Leu Glu Arg Arg Glu Thr Ser Cys
            20                  25                  30

Leu Ala Val His Lys Pro Leu Ile Phe Lys Val Phe Phe Val Leu Phe
        35                  40                  45

Ser Pro Ser Arg Thr Leu Pro Arg Leu Ser Phe Cys Ile Lys His Ser
    50                  55                  60

Gln Phe Phe Trp Leu Ile Leu Cys Thr Lys Tyr Phe Tyr Leu Phe His
65                  70                  75                  80

Ile Leu Arg Leu Phe Leu Gly Tyr Glu Thr Asn Ala Gly Leu Ile Leu
                85                  90                  95

Leu Leu Met Gly Ser Trp Cys Phe Met Trp Leu Ser Lys Leu Cys Arg
            100                 105                 110

Ala Leu Ala Arg Glu Ile Met Leu Leu Gly Leu Val Leu Gly Cys Arg
        115                 120                 125

His Ser Phe Met Leu Met Gly Val Leu Phe Phe Ser Phe Phe Thr Glu
    130                 135                 140

Gln Ser Gln Ala Phe Leu Ile Val Ile Arg Leu Gln Lys His Arg Ser
145                 150                 155                 160

Trp Glu Met Thr Leu Pro Asn Val Glu Met Leu Leu Asn Leu Lys Gly
                165                 170                 175
```


ENSDOCID <WO 0166751A2 >

Ser Phe Leu Tyr Cys Leu Val Leu Cys Phe Ile Leu Ser Glu Asp Cys
180 185 190

Lys Phe Ile Val Ile Lys Lys Asn Pro Arg Ile Thr Arg Ile Pro Phe
195 200 205

<210> 132
<211> 165
<212> PRT
<213> Homo sapiens

<400> 132

Tyr Ala Asn Ile Ser Gln Lys Val Ser Cys Lys Lys Ala Phe Thr Glu
1 5 10 15

His Leu Phe Ile Phe Phe Tyr Asn Tyr Ala Pro Met Ser Thr Val Cys
20 25 30

Gln Thr Pro Arg Ile Arg Arg Arg His Thr Ser Met Asp Glu Trp Leu
35 40 45

Ala Ser Cys Gly Leu Phe Ile Lys Arg Asn Ser Met Leu Arg Lys Thr
50 55 60

Leu Phe Lys Thr Arg Ile His Arg Met Phe Ser Ala Ile Ile Leu Leu
65 70 75 80

Phe Ile Ile Glu Asn Thr Pro Leu His Ile Tyr Val Val Leu Glu Asn
85 90 95

Leu Val Ser Asn Leu Phe Cys Phe Asn Ser Leu Cys Asn Phe Leu Pro
100 105 110

Phe Asn Phe Asn Phe Tyr Phe Met Leu Pro Ile Leu Cys Phe Leu Phe
115 120 125

Phe Leu Leu Leu Val Leu Met Phe Tyr Ser Ile Leu Leu Asn Leu Ile
130 135 140

Lys Val Ile Leu Lys Tyr Phe Pro Tyr Phe Tyr Ser Ile Tyr His Leu
145 150 155 160

Lys Phe Tyr Val Ser
165

<210> 133
<211> 163
<212> PRT
<213> Homo sapiens

<400> 133

Ser Ser Gln Val Ser Tyr Lys Ser Val Thr His Val Ser Gln Ser Ser
1 5 10 15

Asp Met Leu Asn Met Val Leu Val Glu Gln Gln Lys Glu Glu Cys Glu
20 25 30

Glu Ala Ser Arg Tyr Ile Ile His Glu Cys Pro Thr Leu Gly Val Ala
35 40 45

Pro Ser Ala Ile Val Ser Lys Gly His Pro Ser Leu Ile Val Leu Gln
50 55 60

BNSDOCID <WO 0166751A2 I_>

```
Glu Val Pro Val Cys Phe Trp Cys Ser Cys Leu Ile Phe Ser Leu His
65                  70                  75                  80

His Ser Ile Tyr Phe Tyr Arg Glu Glu Glu Ser Ile Thr Leu Ile Tyr
                85                  90                  95

Arg Lys Leu Lys Cys Leu Thr Val Gln Asn Ile Phe Pro Pro Cys Asn
            100                 105                 110

Pro Leu Ser Leu Ile Gly Ala Arg Arg Lys Lys Arg Lys Leu Gly Pro
        115                 120                 125

Gly Lys Leu Gln Gly Pro Trp Glu Gly Arg Lys Gly Leu Ser Leu Met
    130                 135                 140

Leu His Thr Asn Pro Tyr Thr Val Leu Thr Ala Leu Ile Leu Ser Leu
145                 150                 155                 160

Pro Thr Lys
```

<210> 134
<211> 190
<212> PRT
<213> Homo sapiens

<400> 134

```
Leu Glu Arg Ala Lys Val Gly Gly Leu Cys Arg Thr Trp Leu Trp Ala
1               5                   10                  15

Ser Thr Gly Cys Arg Leu Val Pro Met Pro Val Phe Cys His Glu Leu
            20                  25                  30

His Phe Cys Arg Pro Ser Ile Leu Cys Gly Tyr Phe Leu Leu Gln Arg
        35                  40                  45

Phe Arg Pro Arg Arg Arg Leu Phe Val Cys Thr Pro Ser Ala Met Asn
    50                  55                  60

Gly His Ser Ser Cys Leu Leu Gln Met Pro Ser Ser Phe Ala Ala Gly
65                  70                  75                  80

Val Arg Val Leu Ala Ala Leu Leu Gln Met Glu Ile Glu Gln Leu Thr
                85                  90                  95

Cys Tyr Leu Leu Pro Arg Ser His Phe Leu Leu Phe Pro Leu Trp His
            100                 105                 110

His Gln Ala Cys Thr Pro Val Ala Val Glu Gly Leu Asp Ile Pro Ala
        115                 120                 125

Arg Val His Thr His Val Gly Phe Ala Cys Ala Ser Val Arg Pro Leu
    130                 135                 140

Ala Ser Thr His Val Cys Trp Ile Ser Cys Gly Leu Phe Ser Leu Leu
145                 150                 155                 160

Val Leu Ala Leu His Leu Arg Leu Cys Glu Gly Pro Gly Ser Gln Cys
                165                 170                 175

Ser His Leu Arg Thr Gln Ser Pro Glu Gln Asn Phe Ser Phe
            180                 185                 190
```

<210> 135

BNSDOCID <WO 0166751A2_I>

<211> 185
<212> PRT
<213> Homo sapiens

<400> 135

Lys Ser Lys Asn Pro Val Thr Arg Leu Asp Thr Ser Asp Thr Asp His
1 5 10 15

Val Cys His Val His Phe Cys Ile Pro His Lys Ala Pro Tyr Leu Ala
20 25 30

His Ser Thr Cys Ser Leu Thr Leu Asn Glu Tyr Met Thr Gln Pro Gly
35 40 45

Lys Leu Ala Cys Lys Tyr Asn Leu Ile Arg His Asn Asn Ile Trp Gly
50 55 60

Glu Val Arg Pro Ile Pro Thr Thr Ile Asn Tyr Arg Thr Val Ser Val
65 70 75 80

Gly Ala Met Leu Arg Ile Cys Leu Leu Val Ser Ala Gln Glu Arg Val
85 90 95

Asn Ala Ala Gly Met Gly Cys Ser Asn Leu Ala His Ser Lys Glu Arg
100 105 110

Thr Gly Pro Leu Thr Gly Ser Trp Glu Val Thr Phe Glu Pro Leu Glu
115 120 125

Asp Pro Ala Trp Leu Thr Phe Phe Leu Cys Pro Arg Pro Ala Thr Leu
130 135 140

Ser Val Pro Val Cys Ala Asn Lys Val Ile Tyr Gly Glu Cys Leu Val
145 150 155 160

Leu Tyr Ala Gly Pro Ala Trp Ala Val His Gln Gln Phe Asp Leu Ser
165 170 175

Ile Ala Trp Gly Thr Arg Asp Val Ala
180 185

<210> 136
<211> 209
<212> PRT
<213> Homo sapiens

<400> 136

Met Ile Ser Thr Arg Cys Asn Leu Glu Val Gly Asn Ser Val Pro Ser
1 5 10 15

Ser Gln Leu Leu Val Asn Gln Ile Val Asn Leu Thr Asn Leu Phe His
20 25 30

Ile Val Val Ile Gln Asn Leu Pro Glu Leu Arg Ile Tyr Ile Ile Ile
35 40 45

Leu Lys Asn Asn Val Ala Cys Phe Thr Phe Leu Phe Gln Asn Phe Trp
50 55 60

Glu Leu Ile Cys Lys Glu Val Pro Ala Ile Lys Ile Tyr Asn Leu Phe
65 70 75 80

Asn Asn Leu Phe Gly Lys Met His Asp Arg Ala Val Lys Asn Ile Met

BNSDOCID <WO_ 0166751A2_I_>

```
                85                  90                  95

Phe Asp Lys Gly Leu Ile Leu Ser Ala Ala Ser Asp Gly Glu Asn Thr
            100                 105                 110

Lys Cys Leu Gly Ala Val Phe Asn Val Ile Ile Lys Trp Pro Cys Asp
        115                 120                 125

Leu Gln Trp Met Pro Ala Phe His Glu Ala Ser Thr Pro His Arg Met
    130                 135                 140

Ser Lys Ile Ile Leu Thr Ser Thr Ser Phe Gly Tyr Arg Glu Lys Asn
145                 150                 155                 160

Val Lys Glu Cys Asn Ile Leu Arg Glu His Ile Val Leu Tyr Cys His
                165                 170                 175

Asn Lys Ser Asn His Asn Leu His Tyr Glu Asp His Leu Gly Ile Val
            180                 185                 190

Leu Ser Met Thr Leu Arg Asn Arg Arg Glu Phe Gln Leu Cys Leu Leu
        195                 200                 205

Ser
```

<210> 137
<211> 108
<212> PRT
<213> Homo sapiens

<400> 137

```
Thr Ala Pro Cys Phe Leu Ala Leu Cys Ser Met Thr Ser Phe Leu Tyr
1               5                   10                  15

Leu Val Met Ser Met Ser Arg Gly Pro Leu Arg Gly Ile Gly Phe Phe
            20                  25                  30

Ser Cys Phe Ser Ala Leu Cys Cys Gln Val Phe Leu Ala Ser Ala Leu
        35                  40                  45

Met Leu Pro Val Asn Trp Gln Leu Leu His Arg Thr Glu Ile Leu Glu
    50                  55                  60

Ile Trp Tyr Arg Gln Thr Val Glu Val Leu Ser Met Arg Glu Lys Gln
65                  70                  75                  80

Lys Ile Pro Val Glu Lys Lys Gln Lys Ile Pro Phe Cys Leu Ser Pro
                85                  90                  95

Leu Phe Pro Leu Ala Gly Phe Thr Asp Phe Leu Asn
            100                 105
```

<210> 138
<211> 203
<212> PRT
<213> Homo sapiens

<400> 138

```
Val Asn Thr Gln Ile Ser Ile Ser Thr Lys Cys Leu Ser His Trp Ser
1               5                   10                  15

Asn Thr Ser Leu Gly Ala Gly Asp Ser Ser Gly Ser Glu Val Lys Ser
```


BNSDOCID <WO__ 0166751A2 >

20 25 30

Leu Pro Leu Arg Ser Cys Asn Ser Arg Gly Gln Gly Gly Asp Lys Ile
35 40 45

Thr Lys Gln Leu Ser Val Gln Tyr Ile Arg Cys Cys Arg Leu Pro Lys
50 55 60

Leu Ser Gly Phe Thr Gln Asn Pro Ser Ile Ala His Asn Ser Val Cys
65 70 75 80

Arg Asn Trp Gly Leu Ser Lys Val Ser Leu Arg Pro Leu Tyr Leu Pro
85 90 95

Ala Gly Leu Pro Leu Arg Leu Pro Ser Ser Gly Gly Arg Ala Gly Ser
100 105 110

Glu Val Arg Gly Gly Cys Pro Pro Pro Pro Gly Thr Pro Gly Leu Leu
115 120 125

His Thr Cys Leu Ser Pro Lys Gln Gly Cys Leu Arg Leu Gly Ser Gly
130 135 140

Ser Gln Ile Cys Gly Val Leu Glu Ala Leu Glu His Trp Leu Leu Leu
145 150 155 160

Ala Arg Gly Ser Gln Ser Thr Lys Ala Gln Arg Gln Leu His Ala Gly
165 170 175

Arg Gly Ala Gly Arg Leu Arg Trp Trp Leu Gly Pro Gly Val Val Arg
180 185 190

Phe Cys Leu His Pro Ala Gly Gly Asp Arg Ala
195 200

<210> 139
<211> 194
<212> PRT
<213> Homo sapiens

<400> 139

Asn Cys Ser Leu Glu Arg Lys Cys Ser Thr Leu Val Glu Cys Thr His
1 5 10 15

His Lys Ala Val Ser Glu Asn Ala Ser Val Phe Val Cys Glu Asp Ile
20 25 30

Pro Phe Thr Thr Asn Ser Lys Ser Phe Leu Tyr Pro Ala Asp Ser Thr
35 40 45

Lys Asp Val Phe Gln Asn Ser Ser Thr Lys Arg Lys Val Gln Leu Cys
50 55 60

Glu Leu Asn Thr His Ile Thr Lys Glu Phe Leu Arg Met Leu Leu Ser
65 70 75 80

Ser Phe Tyr Val Lys Ile Cys Thr Phe Ser Thr Ile Gly Asn Lys Val
85 90 95

Leu His Met Asn Thr Cys Arg Phe Tyr Lys Lys Gly Val Ser Thr Leu
100 105 110

Val Tyr Gln Lys Lys Val Ser Ser Leu Val Glu Cys Ile His His Lys
115 120 125

BNSDOCID <WO 0166751A2_I_>

Ala Val Ser Glu Asn Ala Ser Val Phe Leu Cys Glu Asp Ile Ser Phe
130 135 140

Ser Ile Leu Gly Leu Lys Ser Leu Gln Ile Ser Thr Cys Arg Tyr Tyr
145 150 155 160

Lys Asn Thr Asp Lys Leu Leu Ser Gln Lys Glu Tyr Ser Asn Leu Val
165 170 175

Glu Cys Ala His His Lys Glu Leu Ser Glu Asn Ala Trp Leu Tyr Phe
180 185 190

Met Asp

<210> 140
<211> 75
<212> PRT
<213> Homo sapiens

<400> 140

Arg Glu Asn Val Glu His Ser Leu Lys Lys Ile Val Thr Leu Ile Phe
1 5 10 15

Lys Arg Gln Phe Phe Leu Asn Ala Leu Pro Leu Met Ile Cys Asp Leu
20 25 30

Cys Val Val Gln Asp Phe Gln Gly Arg Ser Leu Leu Trp Ser Gly Tyr
35 40 45

Ile Tyr Gly Pro His Gln Thr His Ala Glu Ile Ser His Gly Ser Val
50 55 60

Gly Gly Trp Gly Leu Met Gly Gly Val His Val
65 70 75

<210> 141
<211> 224
<212> PRT
<213> Homo sapiens

<400> 141

Cys Phe Ile Tyr Met Lys Ile Gly Val Val Lys Ala Ile Leu Pro Leu
1 5 10 15

Cys Leu Val Ile Ala Ile Ser Val Pro Arg Thr Thr Leu Lys Gly Ser
20 25 30

Leu Asp Gln Arg Lys Phe Ser Val Ser Gly Tyr Ala Ser Pro Glu Leu
35 40 45

Asp Phe Ile Asp Leu Lys Lys Pro His Leu Val Leu Phe Thr Ile Lys
50 55 60

Asp Val Val Pro His Leu His Lys Ile Gln Gly Ser Ile Arg Ile Leu
65 70 75 80

Lys His Val Asp Glu Lys Lys Ile Thr Gly Thr Ile Phe Gln Cys Phe
85 90 95

Thr Ile Cys Leu Ala Gln Tyr Tyr Ile Phe Tyr Arg Cys Ser Cys Pro
100 105 110

BNSDOCID <WO 0166751A2_I>

Lys Thr Leu Asn Ile Asn Cys Tyr Ile Ser Tyr Phe Tyr Phe Ser Asn
115 120 125

Glu Ile Ile Glu Pro Lys Lys Pro Ser Asn Phe Pro Lys Pro Lys Arg
130 135 140

Gln Lys Lys Pro Gly Phe Lys Leu Ser Phe Pro Thr Ala Asn His Cys
145 150 155 160

Leu Ile Trp Tyr Ile Cys Leu Gly Pro Asp Ser Asp His His Arg Ser
165 170 175

Gln Ser Pro Phe Lys Asp Lys Tyr Val Phe Gly Phe Lys Gly Gln Phe
180 185 190

Ile His Phe Ile Asp Lys Lys Ile Glu Ala Gln Lys Asp Thr Arg Trp
195 200 205

Lys Glu His Gln Leu His His Gln Pro Ser Ala Pro Val Leu Ser Val
210 215 220

<210> 142
<211> 143
<212> PRT
<213> Homo sapiens

<400> 142

Pro Asp Ala Glu Pro Ile Thr Thr Asn Ser Thr Leu Met Ala Ser Leu
1 5 10 15

Leu Val Glu Leu Cys Met Val Pro Pro Leu Met Pro Phe Ser Asp Pro
20 25 30

Arg Ala Leu Gln Met Arg Glu Ile Ser Leu Ser Ala Val Ala Ile Val
35 40 45

Pro Ser Ser Pro Gly Arg Gly Arg Arg Leu Arg Gly Ser Pro Ala Ser
50 55 60

Leu Lys Arg Leu Trp Ser Met Lys Pro Pro His Thr Ser Cys Pro Phe
65 70 75 80

Pro Phe Thr Pro Gly Ser Gly Pro Pro Asp His Leu Gln Trp Pro Phe
85 90 95

Pro Ala Ala Ser Trp Arg Ala Gly Cys Leu Ala Phe Cys Leu Asn Thr
100 105 110

Gly Leu Cys Ser His Ile Cys Gln Thr Ser Lys Ala Glu Ala Leu Thr
115 120 125

Leu Gly Arg Tyr His Gly Gly Gly Gly Gly Ser Ala Pro Gly Arg
130 135 140

<210> 143
<211> 213
<212> PRT
<213> Homo sapiens

<400> 143

Ala Ala Asn Leu Asp Ser Gln Ser Glu Tyr Ser Ile Val Ile Ile Arg
1 5 10 15

BNSDOCID <WO 0166751A2_I_>

```
Asn Leu Glu Thr Glu Pro Gly Ala Tyr Glu Phe Asn Lys Gly Trp Leu
            20                  25                  30

Leu Leu Phe Ile Ile Leu Phe Phe Leu Leu Phe Leu Pro Gly Asp Gln
        35                  40                  45

Thr Ser Thr Ala Tyr Phe Ser Pro Tyr Val Thr Thr Arg Ile Phe Pro
    50                  55                  60

Asp Ile Arg Phe Tyr Gln Ile Phe Val Val Thr Tyr Pro Leu Leu Phe
65                  70                  75                  80

Val Cys Ser His Ser Met Val Leu Ile Lys Pro Phe Phe Leu Lys Cys
                85                  90                  95

Phe Ser Val Gly Gln Trp Tyr Leu Ser Asn Ile Leu Asn Phe Leu Lys
            100                 105                 110

Ser His Ser Arg Pro Val Cys Tyr His Leu Val Pro Thr Phe Gln Pro
        115                 120                 125

Ile Phe Pro Thr Thr Pro Pro Tyr Phe Phe Ala Val Thr Lys Ile Asp
    130                 135                 140

Tyr Ser Phe Phe Leu Cys Lys Thr Ala Leu Leu Pro Leu Cys Phe Cys
145                 150                 155                 160

Pro Arg Ala Phe Cys Leu Leu Glu Ser Ser Phe Leu Gln Leu Phe Ile
                165                 170                 175

Pro Tyr Ser Pro Gln Gly Pro Ala Gln Arg Thr Pro Leu Pro Pro Asn
            180                 185                 190

Val Ser Ser Phe Leu Trp Leu Glu Met Ser Ala Val Lys Val Leu Gln
        195                 200                 205

Phe Phe Gly Leu Phe
    210
```

<210> 144
<211> 220
<212> PRT
<213> Homo sapiens

<400> 144

```
Leu Leu Ser Tyr Ile Ser Phe Leu His Cys Cys Ile Ser Cys Ile Ser
1               5                   10                  15

Phe Leu His Leu Ala Asn Ile Ser His Pro Cys Ala Ala Cys Phe Gly
            20                  25                  30

Asp Leu Ser Met Ile Ile Cys Leu Pro Val Ile Leu Asn Phe Glu Arg
        35                  40                  45

His Phe Met Ser Leu Phe Leu Tyr Ser Leu His Cys Val Cys Trp Leu
    50                  55                  60

Thr Asn Tyr Thr Ile Thr Cys Asp Ile Ile Ser Leu Ala Phe Cys Ile
65                  70                  75                  80

Ser Ser Ile Ile Val Leu Lys Leu Ile Ser Ile Ile Gln Leu Asp Leu
                85                  90                  95
```


BNSDOCID <WO 0166751A2_I_>

```
Gly Met Gly Val Phe Glu Phe Leu Cys Glu Val Ala Val Glu Phe His
            100                 105                 110

Phe Ile Tyr Lys Tyr Gly Tyr Phe Phe Gln His Asp Leu Trp Lys His
        115                 120                 125

Ser Thr Phe Ser Tyr Asp Leu Gln Cys Gln Asn Ser Gly Leu Tyr Phe
    130                 135                 140

Trp Thr Pro Cys Tyr Val Ser Ile Gly Phe Met Cys Leu Phe Leu Cys
145                 150                 155                 160

His Tyr Leu Thr Leu Lys Tyr Cys Ser Leu Ile Ile Met Cys His Ile
                165                 170                 175

Phe Ala Met Thr Ser Gln Phe Val Phe Phe Thr Leu Gly Leu Leu His
            180                 185                 190

Phe His Val His Arg Glu Leu Ser Glu Glu Ile Lys Pro Ile Val Ser
        195                 200                 205

Cys Thr Arg Ala Cys Ala His Ser His Val Thr Lys
    210                 215                 220
```

<210> 145
<211> 210
<212> PRT
<213> Homo sapiens

<400> 145

```
Arg Leu Ile Asn Lys Arg Gln Tyr Leu Glu Gln Asn Ile Ile Pro Ile
1               5                   10                  15

Phe Phe Leu Asp Phe Asp Ile Leu Ser Ile Leu Lys Arg Cys Pro Arg
            20                  25                  30

Asn Ile Leu Leu Ser Leu Tyr His Val Pro Gly Gly Asn Ile Pro Asn
        35                  40                  45

Val Leu Phe Lys Phe Ser Val Leu Phe Lys Ser Ala Ile Phe Val Ile
    50                  55                  60

Thr Gln Asn Val Ile Phe Asn Ile Tyr Gln Leu Tyr Lys Ser Asn Leu
65                  70                  75                  80

Glu Phe Arg Ile Thr Lys Thr Lys Ser Phe Tyr His Ser Phe Leu Tyr
                85                  90                  95

Thr Phe Ser Ser Thr His Met Val His Ile Trp Ala Phe Asp Ser Tyr
            100                 105                 110

Val Cys Lys Lys Ile Pro Val Ile Phe Lys Ile Asn Phe Lys Ser Cys
        115                 120                 125

Val Phe Leu Phe Phe Ser His Leu Lys Gly Ile Leu Met Asp Ile Ile
    130                 135                 140

Met Lys Leu Ser Val Lys Val Ile Arg Arg Arg Ile Asp Arg Ile Tyr
145                 150                 155                 160

Ile Tyr Ile Glu Lys Asn His Lys Arg Arg Gln Lys Met Asn Asn Asp
                165                 170                 175

Ile Pro Val Asn Leu Val Leu Cys Thr Leu Pro Leu Ile Ser Phe Ser
```


BNSDOCID: <WO___0166751A2_I_>

180 185 190

Gln Asn Ile Trp Glu Ile Asp Ile Ile Cys His Leu Gln Met Arg Lys
195 200 205

Leu Arg
210

<210> 146
<211> 194
<212> PRT
<213> Homo sapiens

<400> 146

Leu Asn Arg Phe Leu Val Val Lys Leu Leu Ser Cys Val Val Asn Ala
1 5 10 15

Cys Leu Ile Phe Lys Glu Asn Ala Lys Leu Ser Lys Val Ile Arg Ser
20 25 30

Asp His Phe Thr Phe Ser Pro Ala Met Cys Glu Gly Ser Arg Phe Phe
35 40 45

Val Phe Tyr Tyr Ser His Ser Ile Ser Cys Val Leu Leu Ser His Tyr
50 55 60

Gly Phe Asn Leu Tyr Phe Leu Leu Val Phe Leu Leu Leu Cys Asn Lys
65 70 75 80

Leu Pro Gln Thr Gln Leu Lys Thr Thr Phe Phe Leu Phe Thr Val Ser
85 90 95

Met Gly Glu Ser Asp Tyr Arg Leu Thr Arg Val Ser Val Gln Gly Leu
100 105 110

Thr Gly Leu Lys Leu Asn Leu His Gly Thr Ala Val Ser Phe Glu Glu
115 120 125

Phe Leu Leu Gln Ala His Trp Leu Leu Thr Glu Ile Asn Ser Leu Ile
130 135 140

Leu Asp Arg Ser Leu His Phe Leu Phe Gly Tyr Gln Leu Gly Thr Ala
145 150 155 160

Leu Ser Phe Tyr Arg Pro Pro Arg Gly Pro Cys Leu Val Ala Pro Ser
165 170 175

Arg Gly Ser Ser Pro Pro Gly Trp Leu Gln Lys Asn Pro Ser His Phe
180 185 190

Tyr Ser

<210> 147
<211> 133
<212> PRT
<213> Homo sapiens

<400> 147

Leu Val Ile Leu Glu Ile Pro Lys Ser Asn Ser Leu Thr Asn Leu His
1 5 10 15

His Ile Asn Cys Phe Val Ser Asp Gly Leu Phe Gly Ile Asn Phe Lys

ENSDOCID <WO 0166751A2 I >

20 25 30

Ile Asn Gln Leu Arg Cys Leu Glu Ser Cys Thr Leu Val Lys Ile Leu
35 40 45

Tyr Val Asp Thr Met Glu Glu Thr Glu Arg Ala Val Asp Met Ala Ala
50 55 60

Cys Ile Tyr Asp Gly Asn Glu Ser Leu Gly Asn Cys Arg Asp Trp Lys
65 70 75 80

Gly Gly Gln Val Arg Gln Asp Ser Pro Ser Ala Asn Lys Arg Arg Arg
85 90 95

Val Arg Ile Glu Met Leu Ala Arg Ile Lys Val Lys Met Asp Gly Tyr
100 105 110

Ile Trp Ser Gln Leu Asp Phe Gln Glu Tyr Leu Ser Gln Thr Gly Asn
115 120 125

Ile Phe His Phe Ser
130

<210> 148
<211> 163
<212> PRT
<213> Homo sapiens

<400> 148

Cys Gln Arg Asn Ala Gln Arg Asn Cys Ser Leu Glu His Leu Gly Phe
1 5 10 15

Ile Leu Gly Phe Gly Met Leu Asn Val Cys Lys Tyr Pro Lys Ile Lys
20 25 30

Lys Asn Asn Ile Lys His Phe Ser Gln Ala Phe Gln Ile Arg Ser Ala
35 40 45

Pro Thr Cys Ile Ser Cys Leu Val Ile Tyr Leu Ser Leu Tyr Ser Ser
50 55 60

Ile Ser Thr Ser Leu Phe Pro Val His Phe Gln Val Asn Cys Arg Cys
65 70 75 80

Leu Tyr Thr Phe Pro Gly Glu Phe Ser Lys Thr Ile Ser Ser Gln Ala
85 90 95

Ser Ala Gln Arg Cys Thr Asp Leu Leu Ile Gln Glu Phe Phe Gln Thr
100 105 110

Thr Pro Gln Leu His Ser Gly Asn His Ala Asp Gly Ala Leu Ile Ser
115 120 125

Arg Asn Ile Thr Ser Leu Met Ala Lys Gly Lys Asp Leu Ala Tyr His
130 135 140

Val Leu Gly Val Lys Thr Ser Ala Pro Asn Gln Tyr Thr Ser Ala Ser
145 150 155 160

Ala His Ile

<210> 149
<211> 167

BNSDOCID <WO 0166751A2 I >

<212> PRT
<213> Homo sapiens

<400> 149

Ser Leu Thr Arg Ser Thr Ala Lys Glu Thr Met Tyr His Gly Lys Val
1 5 10 15

Leu Asp Thr Val Thr Ala Lys Ile Thr Ser Ala Cys Ser Gly Leu Ser
20 25 30

Leu Lys Ile Cys Pro Leu Gly Cys Gly Glu Leu Cys Ser Cys Val Asn
35 40 45

Leu Glu Leu Arg Ser His His Thr Trp Ile Leu Arg Val Ile Val Ser
50 55 60

Pro Ile Asn Pro Val Phe Phe Ser Ile Pro Leu Ser Thr Leu Asn Val
65 70 75 80

Tyr Gly Phe Phe Thr Phe Cys Leu Pro Lys Pro Ser Arg Asp Ile Asn
85 90 95

Arg Ser Leu Ser Cys Gly Gly Leu Arg Arg Pro Leu Lys Leu Ser Ser
100 105 110

Cys Cys Ser Gln Phe Pro Pro Ile Ala Ile Ser Ser Leu Asn Ile Lys
115 120 125

Ser Ser Ser Gly Val Leu Tyr Gln Ser Leu Leu Leu Lys Thr Asn Thr
130 135 140

Lys Glu Asn Leu Ser Val Phe Phe Ser Leu Phe Phe Cys Leu Thr Phe
145 150 155 160

Lys Lys Phe Phe Arg Ser Tyr
165

<210> 150
<211> 188
<212> PRT
<213> Homo sapiens

<400> 150

Arg Ser His Phe Phe Ser Leu Met Gln Met Ile Glu Asn Asn Leu Asn
1 5 10 15

Ala Asp Gln Gln Gly Thr Gly Ala Ile Tyr Ile Thr Phe Thr Gln Asn
20 25 30

Phe Met Gln Pro Val Lys Asn Lys Ile Asp Leu Tyr Val Leu Ile Arg
35 40 45

Ile Tyr Met Cys Phe Lys Ile Tyr Val Arg Lys Ser Ile Gly Arg Thr
50 55 60

Val Tyr Arg Val Cys Ser His Leu Phe Lys Gly Tyr Arg Cys Ile Tyr
65 70 75 80

Met Tyr Ile Tyr Ile Leu Ser Ile Tyr Ala Asn Leu Ala His Leu Thr
85 90 95

Glu Lys Leu Arg Val Glu Leu Ser Phe Arg Leu Cys Pro Gly Ala His
100 105 110

BNSDOCID <WO 0166751A2 I >

Arg Met Leu Leu Glu Thr Ala Pro His Ser Val Ala Leu His Phe Ser
115 120 125

Leu Cys Trp Leu His Cys Gln Leu Leu Pro Cys His Gly Ser Ser Arg
130 135 140

Leu Ser Gln Leu Leu Gln Phe Met Ala Asp Thr Ile Asp Leu Thr Val
145 150 155 160

Pro Leu Leu Asn Ile Thr Glu Asp Phe Gln Ser Cys Leu Ser Tyr Leu
165 170 175

Pro Ile Leu Trp Ile Pro His Cys Glu Trp Arg Asp
180 185

<210> 151
<211> 131
<212> PRT
<213> Homo sapiens

<400> 151

Arg Gly Arg Ala Leu Ser Gly Ser Leu Gly Leu Asn Leu Val Ala Val
1 5 10 15

Gly Arg Lys Met Cys Glu Gly Pro Gln Cys Trp Gln Asp Leu Ala Tyr
20 25 30

Arg His Glu Leu Leu Ser Gly Ile Trp Gly Arg Val Arg Val Phe Leu
35 40 45

Gly Ala Cys Trp Ile Leu Lys Trp Asn Cys Leu Val Asp Ser Cys Asn
50 55 60

Cys Asp Leu Glu Ser Pro Leu Thr Phe Cys Ser Val Phe Pro Ile His
65 70 75 80

Ser Thr Gly Cys Ile Ser Ser Phe Leu Pro Cys Ser Leu Ser Asp Met
85 90 95

Glu Leu Leu Phe Cys Ser Leu His Arg Pro Glu His Thr Pro Cys His
100 105 110

Ile Asn His Ala Tyr Leu Cys Val Arg Ser Thr Ile Leu Cys Phe Phe
115 120 125

Pro Leu Cys
130

<210> 152
<211> 206
<212> PRT
<213> Homo sapiens

<400> 152

Tyr Gln Gly Tyr Ser Val Cys Leu Phe Tyr Ala Leu Ser His His Leu
1 5 10 15

Val Thr Tyr Lys Thr Ser Glu Thr Gln Ser Tyr His Met Lys Asp Asn
20 25 30

Met Ser His Ser Pro Gly Glu Ala Ile Asp Ile Lys Leu Ala Lys Asn
35 40 45

ENSDOCID <WO__0166751A2_I_>

```
Leu Trp Asp Ser Glu Pro Leu Ile Gln Met Pro Val Thr Gln Met Leu
    50                  55                  60

Ala Leu Lys Ser Ser Phe Pro Thr His Ser Leu Ser Lys Ala Pro Ser
65                  70                  75                  80

Lys Arg Gly Trp Leu Gln Pro Leu Pro Asn Gln Ile Arg Phe His Gly
                85                  90                  95

Gln His Trp Leu Leu Gly Ala Glu Gln Asp Gly Ser Gly Ala Gly Ser
            100                 105                 110

Arg Gly Glu Phe Met Val Ser Met Gln Pro Ala Phe Leu Pro Val Cys
        115                 120                 125

Phe Ala Phe Pro Cys Val Ile Leu Val Phe Trp Phe Val Phe Pro Val
    130                 135                 140

Pro Gln Cys Val Asn Phe Met Asn Thr Tyr Ala Leu Ala Asn Asp Val
145                 150                 155                 160

Leu Ile Arg Arg Ala Val Ala Gly Met Arg Ser Val Leu Cys Leu Gly
                165                 170                 175

Asn Cys Ile Glu Ser Gly Phe Met Leu Ser Asp Ser Phe His Gln Ser
            180                 185                 190

Leu Leu Leu Gly Tyr Trp Glu Glu Leu Val Ile Val Gly Ser
        195                 200                 205
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<210> 153
<211> 130
<212> PRT
<213> Homo sapiens

<400> 153

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Ile Pro Thr Pro Glu Phe Ala Gly Leu Leu Arg Pro Ala Gly Ser Pro
1               5                   10                  15

Ala Arg Leu Thr Ser Trp Thr Ala His Leu Asp Ser Trp Arg Gly Lys
            20                  25                  30

Gly Ile His Pro Arg Phe Gly Asn Phe Thr His Arg Ala Phe Arg Gly
        35                  40                  45

Val Glu Arg Val Met Glu Thr Asn Lys Ala Gly Glu Ala Pro Arg His
    50                  55                  60

Gln Lys Glu Ala Val Thr Thr Ser Met Ala Val Arg Thr Arg Gly Asp
65                  70                  75                  80

Asn Cys Thr His Arg Ala Pro Trp Gly Leu Glu Pro Trp Ser Lys Ser
                85                  90                  95

Tyr Leu Gly Gly Thr Gly Val Leu Glu Gly Cys Arg His Cys Gln Lys
            100                 105                 110

Arg Pro Ser Thr Pro Gly Glu Glu Leu Gly Arg Gly Thr Pro Ala Thr
        115                 120                 125

Phe Pro
    130
```


ENSDOCID <WO 0166751A2_I_>

<210> 154
<211> 87
<212> PRT
<213> Homo sapiens

<400> 154

Arg Gly Pro Ile Cys Trp Ile Ala Ile Ile Gln Val Asn Arg Ser Arg
1 5 10 15

Pro Val Cys Thr Ser Gln Glu His Val Pro His Ile Leu Gly Asp Val
20 25 30

Leu Asn Trp Ala Arg Tyr Arg Val Gln Leu Asn Ile Tyr Cys Leu Asp
35 40 45

Leu Asp Pro Pro Pro Gly Gln Asp Ala Thr Leu Glu Pro Ser Arg Gly
50 55 60

Pro Arg Ala Trp Pro Ser Cys Ser Phe His Leu Thr Gly Gln Glu Ala
65 70 75 80

Glu Val Lys Ala Pro His Gly
85

<210> 155
<211> 205
<212> PRT
<213> Homo sapiens

<400> 155

Phe Gln His Asp Leu Trp Lys His Ser Thr Phe Ser Tyr Asp Leu Gln
1 5 10 15

Cys Gln Asn Ser Gly Leu Tyr Phe Trp Thr Pro Cys Tyr Val Ser Ile
20 25 30

Gly Phe Met Cys Leu Phe Leu Cys His Tyr Leu Thr Leu Lys Tyr Cys
35 40 45

Ser Leu Ile Ile Met Cys His Ile Phe Ala Met Thr Ser Gln Phe Val
50 55 60

Phe Phe Thr Leu Gly Leu Leu His Phe His Val His Arg Glu Leu Ser
65 70 75 80

Glu Glu Ile Lys Pro Ile Val Ser Cys Thr Arg Ala Cys Ala His Ser
85 90 95

His Val Asn Lys Asn His Thr Ser Val Asp Phe Leu Phe Tyr Asn Phe
100 105 110

Thr Lys Leu Ile Asp Gln Phe Glu Lys Thr Gln His Phe Ser Tyr Ile
115 120 125

Lys Ser Phe Asn Ser Cys Ile Tyr His Ile Asn Val Phe Leu Ile Ile
130 135 140

Ser Asp Phe Leu His Lys Asp Ile Ala Leu Leu Leu Ile Asp Leu Leu
145 150 155 160

Val Gly Val Leu Cys Ile Arg Asn Cys Lys Cys His Ile Phe Ile Ile
165 170 175

BNSDOCID <WO 0166751A2>

```
Phe Ser Lys Tyr Phe Ser Ile Val Thr Phe Glu Asp Ile Asp Ile Asn
            180                 185                 190

Phe Phe Met Asn Ile Cys Thr Val Leu Leu Glu Gln Phe
        195                 200                 205
```

<210> 156
<211> 148
<212> PRT
<213> Homo sapiens

<400> 156

```
Val Thr Thr Thr Glu Ile Arg Leu Ile Pro Asp Pro Lys Asn Leu His
1               5                   10                  15

His Val Phe Ser Arg Ser Ile Ser Thr Leu Lys Ala Thr Gly Ser Leu
            20                  25                  30

Ile Asn Leu His Gly Leu Val Leu Pro Leu Ser Glu Leu His Ile Ser
        35                  40                  45

Arg Ile Ala Cys Ser Phe Gly Val Val Cys Cys Phe Gln His Val Trp
    50                  55                  60

Arg Ser Ser Tyr Val Val Val Cys Ser Asn Ser Ser Leu Phe Leu Ile
65                  70                  75                  80

Ala Ile His Phe Asn Ile Trp Thr Ile Thr Glu Cys Ser Asn Ser Ser
                85                  90                  95

Leu Phe Leu Ile Ala Ile His Phe Asn Ile Trp Thr Ile Thr Glu Phe
            100                 105                 110

Ile Leu Leu Arg Met Asp Val Ala Val Trp Gly Tyr His Tyr Asn Tyr
        115                 120                 125

Leu Cys Glu Ile Phe Cys Ala Cys Thr Leu Asp Ala Gly Gln Val Ser
    130                 135                 140

Pro Lys Met Gly
145
```

<210> 157
<211> 117
<212> PRT
<213> Homo sapiens

<400> 157

```
Trp Ala Lys Trp Leu Tyr Tyr Pro Phe Tyr Gly Ser Asn Thr Ser Lys
1               5                   10                  15

Ser Gly Ser Leu Gln Ile Ser Lys Phe Ser Leu Leu Val Pro Glu Ile
            20                  25                  30

Val Gln Val Asn Asn Asn Thr Ser Asn Asn Phe Ile Tyr His Ile Gly
        35                  40                  45

Asp Leu Ser Arg Leu Asn Ala Val Tyr Phe Leu Lys Ile Ile Thr Val
    50                  55                  60

Leu Asn Asn Ala Arg Val Leu Arg Ser Tyr Tyr Leu Lys Lys Asn Val
65                  70                  75                  80
```


ENSDOCID <WO 0166751A2 I

Phe Tyr Asn Ser Gln Leu Lys Glu Pro Ala Arg Lys Phe Asn Gln Gly
85 90 95

Lys Gln Ser Leu Lys Asn Thr Glu Met Asn Asp Ile Ile Lys Leu Tyr
100 105 110

Pro Lys Cys Ile Ala
115

<210> 158
<211> 209
<212> PRT
<213> Homo sapiens

<400> 158

Val His Arg Gly Leu Leu Tyr Ser Ala Gly Thr Val Val Ser Leu Gln
1 5 10 15

Ala Pro Val Val Leu Arg Ser Cys Leu Cys Ala Glu Tyr Cys His Ala
20 25 30

Glu Leu Glu Gly Arg Gly Thr Ser Ser Gln Val Met Gly His Pro Leu
35 40 45

Asn Ile Trp Ser Thr Asp Arg Thr Val Ala Arg Arg Val Trp Ala Pro
50 55 60

His Thr Asp Arg Ser Ser Leu Gly Ile Ala Leu Gly Leu Ser Pro Gly
65 70 75 80

Pro Gly Thr Lys Gly Ala Glu Gly Glu Ser Ile Ser Leu Ser Gly Arg
85 90 95

Lys Lys His Ser Ser Lys Gly Ser Gly Leu Arg Pro Phe Leu Lys Arg
100 105 110

Thr Gly Glu Phe Ile Tyr Leu Arg Ser Ser Cys Ile Asn Val Lys Gly
115 120 125

Leu Ala Thr Pro Phe Asn Leu Gln Cys Arg Asp Gly Val Ile Cys Ser
130 135 140

Val Trp Lys Ser Pro Arg Gly Glu Gly Ala Leu Cys Leu Ser Val His
145 150 155 160

Ile Ile Gln Thr Glu Met Ala His Asp Gly Cys His Val Thr Pro Gly
165 170 175

Thr Thr Val Ala Ser Thr Leu Ser Ser Thr Gln His Thr Thr Pro Pro
180 185 190

Thr Val Ser Leu Phe Leu Pro Leu Phe Pro Leu Ala Cys Leu Phe Phe
195 200 205

Ser

<210> 159
<211> 158
<212> PRT
<213> Homo sapiens

<400> 159

BNSDOCID <WO 0166751A2 I >

```
Gly Ile Leu Asp Pro Ser Leu Asn Leu Ile Thr Asn Trp Asp Tyr Trp
1               5                  10                  15

Asp Leu Tyr Cys Lys Val Thr Ile Phe Leu Phe Val Thr Asn Lys Tyr
            20                  25                  30

Gln Arg Gly Tyr Thr Leu Arg Leu Cys Glu Tyr His Phe Ser Arg His
        35                  40                  45

Ala Phe Ala His Ser Phe Gln His Pro Leu Ile Phe Ala Ser Thr Tyr
    50                  55                  60

Tyr Ser Gly Val Cys Leu Phe Pro Ser Ser Leu Leu His Leu Met Ile
65                  70                  75                  80

Arg Ile Leu Pro Arg Ser Ala Phe Pro Thr Leu Gln Phe Ile Tyr Val
                85                  90                  95

Ile Ile Tyr Ser Cys Met Pro Val Trp Thr Ser Gly Tyr Phe Phe Ile
            100                 105                 110

Leu Cys Val Val Met His Tyr Tyr His Tyr Leu Phe Cys Cys Pro Ala
        115                 120                 125

Trp Pro Arg Phe Gly His Gly Leu Leu Gln Ala Gly Ser Tyr Val Leu
    130                 135                 140

Leu Ala Cys Pro Ser Ser Ser Pro Gln Pro Ser Asn Leu Leu
145                 150                 155

<210>  160
<211>  190
<212>  PRT
<213>  Homo sapiens

<400>  160

Gln Gln Val Gly Cys Arg Ala Lys Met Leu Arg Leu His Ile Ala Gly
1               5                  10                  15

Gly Pro Gly Ala Gln Pro Thr Gln Pro Ile Phe Ser Thr Arg Pro Leu
            20                  25                  30

Ala Cys Asp Gly Arg Gly Cys Cys Lys Gly Leu Cys His Ala Leu Glu
        35                  40                  45

Thr Phe Ser Pro Leu Ser Trp Leu Thr Phe Gly Ser Leu Leu Leu Met
    50                  55                  60

Gln Asn Phe Cys Ser Trp Leu Glu Phe Pro Pro Arg Lys Trp Gly Phe
65                  70                  75                  80

Leu Phe Tyr His Ile Phe Arg Leu Gln Val Phe Pro Asn Phe Tyr Ala
                85                  90                  95

Leu Leu Pro Leu Lys Cys Phe Asp Thr Glu Ile Ser Ser Thr Arg Ile
            100                 105                 110

His Ile Ile Thr Leu Ser Phe Lys Val Pro Thr Asp Leu Gly Arg Gly
        115                 120                 125

Lys Asn Ala Ala Ser Leu Phe Ala Gln Glu Pro Leu Leu Phe Pro Asn
    130                 135                 140

Lys Phe Ser His Leu His Leu Arg Pro Pro Gln Pro Gly Pro Tyr Cys
```


BNSDOCID <WO 0166751A2_I_>

145 150 155 160

Pro Tyr His Asn Gln His Phe Gly Lys Ser His Ser Thr Ser Leu Trp
165 170 175

Glu Val Pro Asn Phe Ser Arg Ser Phe Cys Leu Leu Ser Pro
180 185 190

<210> 161
<211> 126
<212> PRT
<213> Homo sapiens

<400> 161

Pro Cys Leu Leu Lys Thr Leu Gln Gly Leu Pro Val Ala Leu Arg Ile
1 5 10 15

Gln Tyr Arg Ser Leu Pro Gly Glu Pro Gln Gly Ser Ala Ser Gly Pro
20 25 30

Ala Cys Cys Leu Ser Cys His Ser Gly Pro His Leu Arg Val Leu Phe
35 40 45

Gly Ser Ser Val Ser Phe Ser His Ser Val Pro Ser Ser Tyr Thr Leu
50 55 60

Phe Pro Leu Pro Ala Leu Pro Ser Ser Pro Ser Ser His Glu Phe Gly
65 70 75 80

Leu Pro Ala Cys Pro Ser Glu Ser Leu Leu Pro Tyr Thr Phe Lys Leu
85 90 95

Leu Leu Lys Cys Tyr Leu Phe Ile Glu Met Ile Ser Asp Phe Leu Tyr
100 105 110

Tyr Tyr Tyr His Tyr Phe Phe Glu Thr Trp Ser His Ser Leu
115 120 125

<210> 162
<211> 69
<212> PRT
<213> Homo sapiens

<400> 162

Pro Trp Ile Ala Leu Ser Ala Trp Thr His Pro Leu Leu Leu Val Thr
1 5 10 15

Leu Thr Phe Pro Ser Leu Thr Gly Gln Ser Ala Cys Tyr Leu Phe Ser
20 25 30

Pro Trp Thr Ala Cys Pro Pro Gly Trp Pro Phe Arg Trp Ser Gln Val
35 40 45

Pro Pro Ser Val Ile Pro Ser Gly Ile Gln Ala Leu Asp Ala Leu Gly
50 55 60

Gly Tyr Leu Cys Thr
65

<210> 163
<211> 201
<212> PRT
<213> Homo sapiens

ENSDOCID <WO_ 0166751A2_I_>

<400> 163

Leu Phe Leu His Lys Asn Ser Phe Cys Val Val Lys Ala Pro Cys Phe
1 5 10 15

Asp Lys Gln Gln Lys His Phe Gln Lys Pro Leu Ser Asn Asn Ser Val
20 25 30

Ser Gln Gly Asn Arg Ile Ile Lys Ser Thr Asn Ala Ala Thr Ile Leu
35 40 45

Phe Asn Val Pro Phe Ser Cys Val Phe Phe Met Thr Cys Leu Gly Ile
50 55 60

Ile Tyr Leu Ser Trp Ser Cys Asn Ser Ile Cys Ile His Leu Asn Arg
65 70 75 80

Leu Thr Trp Arg Val Phe Ile Phe Ser Leu Ser Thr Cys Thr Phe His
85 90 95

Pro Cys Cys Leu Thr Ala Arg Ser Ser Gly Glu Lys Arg Glu Leu Asp
100 105 110

Thr Asp Phe Glu Val Arg Gly Lys Gly Leu Lys Phe Leu Lys Ser Arg
115 120 125

Glu Val Gly Tyr Val Ser Thr Asn Ile Leu Phe Phe Gln Gln Met Ser
130 135 140

His Leu Arg Thr Thr Lys Asp Asn Pro Lys His Ser Leu Tyr Leu Phe
145 150 155 160

Thr Ser Leu Phe Lys Val Ile Arg Ile Lys Cys Glu Val Ser Ser Ser
165 170 175

Ser Cys Ser Arg Leu Leu Val His Leu Gln Tyr Lys Ser Arg Ile Lys
180 185 190

Ser Asn His Lys Val Ile Gln Asp Cys
195 200

<210> 164
<211> 179
<212> PRT
<213> Homo sapiens

<400> 164

Ala Glu Thr Cys Leu Ala Leu Gln Pro Gly Gln Gln Glu Asn Ser Ile
1 5 10 15

Ser Lys Lys Lys Lys Lys Arg Arg Glu Ala Phe Ser Val Phe Ser Thr
20 25 30

Lys Lys Ile Ala Ser Phe Phe Phe Val Ala Trp Ile Ser Tyr Ile Thr
35 40 45

Pro Leu Tyr Lys Phe Gly Ser Gly His Val Gln Met Ile Gln Phe Lys
50 55 60

Ile Leu Ile Pro Phe Leu Ser Tyr Gln Lys Tyr Leu Ile Leu Ser Asn
65 70 75 80

Leu Tyr Gly His Ile Leu Trp Lys Gly Lys Cys Thr Leu Ile Pro Ser

ENSDOCID <WO 0166751A2 I>

85 90 95

Ile Tyr Ile Ile Asp Asp Phe Phe Gly Val Cys Pro Arg Asn Thr Val
100 105 110

Cys Tyr Ile Val Gly Arg Ser Ser Arg Met Ser Lys Thr Ala Ser Asp
115 120 125

Pro Phe Val Ile Leu Leu Lys Pro Leu Leu Ile Tyr Met Phe Leu Phe
130 135 140

Lys Phe Leu Glu Ile Asn Gln Met Tyr Ile Phe Glu Ile Pro Phe Leu
145 150 155 160

Lys Ile Ile Phe Phe Asn Asn Tyr Asn Tyr Lys Trp His Cys Cys Val
165 170 175

Thr Cys Ser

<210> 165
<211> 146
<212> PRT
<213> Homo sapiens

<400> 165

Phe Cys Ile Ser Phe Ile Ile His Pro Thr Leu Val Pro Leu Leu Leu
1 5 10 15

Cys Ser Phe Ser Leu Pro Leu Thr Leu Thr Thr Phe Ser Leu Leu Tyr
20 25 30

Asn Tyr Phe Phe Leu Phe Phe Leu Phe Val Trp Gly Ala Cys Ala Gly
35 40 45

Ser Leu Gln Arg Ile Cys Val Met Gly Val Cys Cys Ala Asp Tyr Phe
50 55 60

Thr Ile Trp Val Leu Ser Leu Val Pro Cys Thr Val Ile Phe His Val
65 70 75 80

Ile Phe Leu Ser Ile Lys Ser Gly Lys Met Tyr Ser Ile Tyr Met Asn
85 90 95

Ile Pro Cys Leu Ser Thr Leu Val Glu Phe Met Leu Ile Asn Ser Phe
100 105 110

Phe Phe Pro Tyr His Trp Gln Trp Asn Lys Thr Lys His Leu Phe Leu
115 120 125

Cys Cys Tyr Gln His Ile Glu Leu Thr Glu Ser Phe Asp Lys Phe Ser
130 135 140

Lys Tyr
145

<210> 166
<211> 206
<212> PRT
<213> Homo sapiens

<400> 166

Ser Ile Val Ile Ile Arg Asn Leu Glu Thr Glu Pro Gly Ala Tyr Glu

BNSDOCID <WO 0166751A2_I_>

```
1               5                   10                  15

Phe Asn Lys Gly Trp Leu Leu Leu Phe Ile Ile Leu Phe Phe Leu Leu
            20                  25                  30

Phe Leu Pro Gly Asp Gln Thr Ser Thr Ala Tyr Phe Ser Pro Tyr Val
        35                  40                  45

Thr Thr Arg Ile Phe Pro Asp Ile Arg Phe Tyr Gln Ile Phe Val Val
    50                  55                  60

Thr Tyr Pro Leu Leu Phe Val Cys Ser His Ser Met Val Leu Ile Lys
65                  70                  75                  80

Pro Phe Phe Leu Lys Cys Phe Ser Val Gly Gln Trp Tyr Leu Ser Asn
                85                  90                  95

Ile Leu Asn Phe Leu Lys Ser His Ser Arg Pro Val Cys Tyr His Leu
            100                 105                 110

Val Pro Thr Phe Gln Pro Ile Phe Pro Thr Thr Pro Pro Tyr Phe Phe
        115                 120                 125

Ala Val Thr Lys Ile Asp Tyr Ser Phe Phe Leu Cys Lys Thr Ala Leu
    130                 135                 140

Leu Pro Leu Cys Phe Cys Pro Arg Ala Phe Cys Leu Leu Glu Ser Ser
145                 150                 155                 160

Phe Leu Gln Leu Phe Ile Pro Tyr Ser Pro Gln Gly Pro Ala Gln Arg
                165                 170                 175

Thr Pro Leu Pro Pro Asn Val Ser Ser Phe Leu Trp Leu Glu Met Ser
            180                 185                 190

Ala Val Lys Val Leu Gln Phe Phe Gly Leu Phe Leu Cys Cys
        195                 200                 205

<210>  167
<211>  197
<212>  PRT
<213>  Homo sapiens

<400>  167

Ile Tyr Phe Ser Ile Ile Gln Thr Lys Asp Pro Leu His Thr Leu Tyr
1               5                   10                  15

Ile Ile Phe Ser Gly Cys Leu Ile Ser Ser His His Phe Ile Gly Lys
            20                  25                  30

Lys Asn Lys Ile Lys Met Glu Lys Asn Leu Phe Lys Leu Phe Leu Val
        35                  40                  45

Ala Phe Thr Phe Ser Phe Lys Leu His Ser Tyr Glu Val Phe Ile Leu
    50                  55                  60

Ser Lys Glu Ala Lys Leu Phe Lys Ser His Gln Leu Ile Thr Lys Pro
65                  70                  75                  80

His Phe Ile Pro Ser Ser Ser Ser Ile Pro Ser Leu Ile Pro Ser Ser
                85                  90                  95

Met Val Ser Leu Leu Gly Leu Leu Gly Thr Thr Leu Ser Trp Ile Leu
            100                 105                 110
```


ENSDOCID <WO 0166751A2 I

Phe Cys Leu Pro Ala Leu Ser Ser Ser Tyr Leu Leu Cys Ile Phe Cys
115 120 125

Ile His Pro Gly Ser Thr Leu Leu Ser Ala Leu Gly Leu Asn Ser Cys
130 135 140

Ala Phe Leu His Leu Phe Pro Leu Thr Ala Ser Ile Tyr Leu Arg Arg
145 150 155 160

Val Asn Leu Gln Ile Phe Leu Asn Leu Gly Ser Ile Ile Ser Thr Trp
165 170 175

Met Ser Trp Val Leu His Ile Leu Thr Gly Ile Ser Ser Cys Arg Asp
180 185 190

Tyr Ser Thr His Arg
195

<210> 168
<211> 192
<212> PRT
<213> Homo sapiens

<400> 168

Ser Val Trp Phe Cys Glu His Ile Ser Phe Ser Ile Ile Gly Leu Ile
1 5 10 15

Pro Gln Ile Tyr Thr Cys Arg Tyr Tyr Lys Lys Asn Cys Phe Lys Leu
20 25 30

Leu Ser Arg Lys Glu Cys Ser Thr Leu Val Glu Cys Thr His His Lys
35 40 45

Ala Val Ser Glu Asn Ala Ser Val Phe Val Cys Glu Asp Ile Pro Phe
50 55 60

Thr Thr Asn Ser Lys Ser Phe Leu Tyr Pro Ala Asp Ser Thr Lys Asp
65 70 75 80

Val Phe Gln Asn Ser Ser Thr Lys Arg Lys Val Gln Leu Cys Glu Leu
85 90 95

Asn Thr His Ile Thr Lys Glu Phe Leu Arg Met Leu Leu Ser Ser Phe
100 105 110

Tyr Val Lys Ile Cys Thr Phe Ser Thr Ile Gly Asn Lys Val Leu His
115 120 125

Met Asn Thr Cys Arg Phe Tyr Lys Lys Gly Val Ser Thr Leu Val Tyr
130 135 140

Gln Lys Lys Val Ser Ser Leu Val Glu Cys Ile His His Lys Ala Val
145 150 155 160

Ser Glu Asn Ala Ser Gly Phe Leu Trp Glu Asp Ile Ser Phe Ser Ile
165 170 175

Leu Gly Leu Asn Arg Ser Asn Ile His Leu Gln Val Leu Gln Lys His
180 185 190

<210> 169
<211> 167
<212> PRT

BNSDOCID <WO 0166751A2_I_>

<213> Homo sapiens

<400> 169

Thr Gln Asn Leu Gln Arg Leu Leu Ile Thr Thr Asn Pro Lys Val Ile
1 5 10 15

Thr Asn Pro Pro Ser Leu Thr Ser Val Leu Phe Val Leu Gln His Phe
20 25 30

Phe Tyr Phe Phe Asn Tyr Asn Gly Cys Phe His Val Ser Leu His Leu
35 40 45

Tyr Met Leu Ile Val Leu Thr Glu Gly Pro Ser Leu Thr Phe His Ser
50 55 60

Cys Trp Glu Ile His Ala Ser Ser Thr Glu Ile Ile Phe Leu Thr Ser
65 70 75 80

Leu Ser Arg Met Asn Trp Leu Phe Ile Cys Thr Pro Thr Glu His Phe
85 90 95

Leu Asn Leu Lys Asn Ser Thr Ile Lys Leu Arg Asn Gly Ala Arg Tyr
100 105 110

Ser Gly Tyr Thr Ala Met Pro Gly Thr Val Thr Met Ser Asn Cys Leu
115 120 125

Asn Leu Thr Asn Thr Asp Ile Val Leu Ile Phe Lys Val Leu Leu Val
130 135 140

Phe Tyr Lys Asp Gln Leu Ile Ser Ser Trp Lys Leu Met Lys Val Leu
145 150 155 160

Leu Val Phe Pro Pro Asn Arg
165

<210> 170
<211> 158
<212> PRT
<213> Homo sapiens

<400> 170

Gln Tyr Ile Arg Cys Cys Arg Leu Pro Lys Leu Ser Gly Phe Thr Gln
1 5 10 15

Asn Pro Ser Ile Ala His Asn Ser Val Cys Arg Asn Trp Gly Leu Ser
20 25 30

Lys Val Ser Leu Arg Pro Leu Tyr Leu Pro Ala Gly Leu Pro Leu Arg
35 40 45

Leu Pro Ser Ser Gly Gly Arg Ala Gly Ser Glu Val Arg Gly Gly Cys
50 55 60

Pro Pro Pro Pro Gly Thr Pro Gly Leu Leu His Thr Cys Leu Ser Pro
65 70 75 80

Lys Gln Gly Cys Leu Arg Leu Gly Ser Gly Ser Gln Ile Cys Gly Val
85 90 95

Leu Glu Ala Leu Glu His Trp Leu Leu Leu Ala Arg Gly Ser Gln Ser
100 105 110

ENSDOCID <WO 0166751A2 I >

Thr Lys Ala Gln Arg Gln Leu His Ala Gly Arg Gly Ala Gly Arg Leu
115 120 125

Arg Trp Trp Leu Gly Pro Gly Val Val Arg Phe Cys Leu His Pro Ala
130 135 140

Gly Gly Asp Arg Ala Cys Cys Met Gly Leu Leu Ala Trp Glu
145 150 155

<210> 171
<211> 210
<212> PRT
<213> Homo sapiens

<400> 171

Glu Ile Gln Lys Phe Phe Phe Ser Phe Leu Ser Gln Leu Arg Ser Trp
1 5 10 15

Glu Phe Ala Pro Cys Gln Leu Glu Thr Met Ile Phe Lys Arg Ile Gln
20 25 30

Ala Leu Leu Thr Ile Arg Gln Asp Tyr Tyr Ile Ser Val Ser Met Arg
35 40 45

Ile Glu Ala Pro Gln Lys His Gln Phe Leu Thr Ser Val Gln Asp Met
50 55 60

Glu Pro Leu Leu Phe Tyr Leu Arg Phe Tyr Phe Ser Arg Thr Ser Arg
65 70 75 80

Ser Ser Phe Ser Arg Phe Tyr Phe Glu Glu Leu Leu Glu His Ser Tyr
85 90 95

Leu Ala Val Phe Arg Arg Glu Ala Asn Phe His Leu Phe Gly Glu Arg
100 105 110

Arg Trp Ala Leu Asn Thr Phe Gln Phe Glu Asp Gly Val Leu Leu Glu
115 120 125

Ile Val Leu Gln Val Ala Ile Tyr Lys Met Phe His Cys Gly Asn Lys
130 135 140

Glu Lys Gly Ser Val Arg Arg Thr Gly Phe Leu Ser Trp Leu Ser Ala
145 150 155 160

Asn Tyr Leu Tyr Gly Phe Gly Glu Val Ile Leu Cys Leu Ser Gln Leu
165 170 175

Ser Phe Ser Ala Pro Leu Gly Arg Gln Gly Tyr Lys Leu Ser Tyr Ser
180 185 190

Gln Arg Cys Leu Ser Pro Leu Val Tyr Tyr Thr Ser Cys Asn Leu Phe
195 200 205

Lys Lys
210

<210> 172
<211> 136
<212> PRT
<213> Homo sapiens

<400> 172

ENSDOCID <WO 0166751A2_I >

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Thr Gln Phe Val Phe Lys Thr Val Thr Phe Ser Phe Tyr Asn Thr Ile
1               5                  10                  15

His Arg Thr Lys Asn Thr Lys Gly Leu Cys Val His Val Ser Trp Ile
            20                  25                  30

Thr Ser Ala Val Ile Trp Cys Ser Ala Ser Leu Cys Trp Val Lys Met
        35                  40                  45

Val Gln Gln Asn Phe Trp Lys Arg Lys Gln Pro Ile Thr Tyr Leu Gln
    50                  55                  60

Val Leu Gln Val Leu Gly Gly Val Val Ser Thr Ile Trp Pro Gly Gly
65                  70                  75                  80

Val Pro Gln Ser Glu Cys Ser Leu Ala Phe Leu Ser Ile Thr Pro Trp
                85                  90                  95

Pro Leu Lys Tyr Phe Ile Lys Glu Gly Pro Gly Ile His Phe Asp Leu
            100                 105                 110

Cys Lys Val Trp Glu Lys Glu Lys His Pro Val Ile Arg Phe Arg Ile
        115                 120                 125

His Arg Arg Ser Ser Phe Asp Thr
    130                 135
```

<210> 173
<211> 170
<212> PRT
<213> Homo sapiens

<400> 173

```
Arg Ile Tyr Thr Ile Lys Lys Lys Pro Asp Leu Glu Met Asn Gln Lys
1               5                  10                  15

Lys Tyr Phe Lys Arg Lys Ile Ile Ile Ile Ala Val Lys Ser Thr Ser
            20                  25                  30

Ile Ser Glu Ser Arg Ser Glu Pro Ala Glu Lys Asn Ile Gln Ser Thr
        35                  40                  45

Lys Leu Ala Arg Val Ala Gln Arg Gly Gly Gly Ala Glu Asp Arg Ala
    50                  55                  60

Ile Glu Arg Ser Pro Pro Arg Arg Met Cys Cys Gly Val Val Val Lys
65                  70                  75                  80

Arg Glu Leu Arg Gly Leu Pro Glu Gly Glu Glu Thr Ser Asp Phe Glu
                85                  90                  95

Met Glu Gln Val Leu Asn Lys Ile Asn Lys Met Asn Ser Pro Pro Glu
            100                 105                 110

Arg Asn Tyr Ser Val Pro Gln Thr Val Leu Leu Ile Glu Glu Asp Thr
        115                 120                 125

His Val Cys Phe Val Ala Phe Cys Gly Pro Tyr Leu Ser Cys Ser Ala
    130                 135                 140

Tyr Pro Glu Glu Ala Arg Arg Ile Ala Leu Arg Leu Ala Ser Gly Asp
145                 150                 155                 160

Arg Ile Leu Thr Val Tyr Pro Gly Ser Trp
```


RNSDOCID <WO 01667514 >

165 170

<210> 174
<211> 161
<212> PRT
<213> Homo sapiens

<400> 174

Glu Arg Glu Lys Ile Ile Tyr Leu Gly Val Thr Val Thr Ile Ser Lys
1 5 10 15

Ser Ile Pro Asp Phe Ser Leu Lys Gly Leu Gly Cys Pro Leu Ser Asp
20 25 30

Lys Phe Pro Asp Leu Thr Glu Arg Leu Pro Ser Ala Met Lys Ile Gln
35 40 45

Leu Met Lys Phe Lys Arg Cys Trp Cys Thr Ser Tyr Ser Asn Arg Arg
50 55 60

Val Arg Met Cys Asp Ser Lys Leu His Ser Val Gln Phe Leu Pro Ile
65 70 75 80

Ser Cys Leu Leu Phe Tyr Leu Cys Leu Trp Phe Trp Ser Leu Ala Ala
85 90 95

Ala Asp Ser Trp Gln Asn Pro Arg Ala Trp Ile Arg Arg Leu Ser Leu
100 105 110

Ser Phe Ile Ile Ala Phe Phe Phe Val Ala Ile Ile Ser Ile Pro Val
115 120 125

Cys His Val Ile Val Thr Thr Pro Cys Thr Val Val Gly Gly Ile Lys
130 135 140

Ser Asp Gly Ile Glu Tyr Phe Val Lys Thr Val Thr Tyr Asp Val Thr
145 150 155 160

Val

<210> 175
<211> 183
<212> PRT
<213> Homo sapiens

<400> 175

Arg Trp Ile Asp Arg Ile Asp Arg Ile Glu Leu Glu Asn Thr Tyr Leu
1 5 10 15

Phe Ser Leu Gly Gly Ile Val Gly Leu Leu Trp Gly Phe Pro Phe Ala
20 25 30

Leu Leu Phe Leu Asp Asn Phe Tyr Thr Phe Ser Cys Ile Phe Leu Thr
35 40 45

Lys Phe Ser Leu Arg Phe Leu Gln Val Phe Leu Phe Leu Ser Asn Ser
50 55 60

Phe Pro Asn Thr Arg Asn Ser Gln Cys Ser Trp Tyr Val Cys Val Ser
65 70 75 80

Val Cys Leu Leu His Val Ser Val Val Cys Val Ser Val Val Cys Val

BNSDOCID <WO 0166751A2_I_>

85 90 95

Tyr Cys Met Cys Leu Tyr Val Val Cys Val Leu Ala Trp Thr His Trp
100 105 110

His Gln Ala Phe Phe Phe Phe Ile Phe Pro Ser Phe Leu Ser Ser Gln
115 120 125

Lys Ile His Lys Leu Ile Phe Glu Gly Arg Arg Gln Ala Tyr Tyr Asn
130 135 140

Leu Leu Pro Thr Phe Pro Tyr Leu Asn Met Val Ile Gly Tyr Trp Leu
145 150 155 160

Leu Ile Thr Leu Asn Ser Glu His Phe Ile His Ser Lys Pro Ala Ser
165 170 175

Ala Leu Leu Lys Asn Met Ile
180

<210> 176
<211> 202
<212> PRT
<213> Homo sapiens

<400> 176

Ile Thr Leu Lys Thr Asn Ile Phe Leu Ala Ser Cys Ser Ser Ser His
1 5 10 15

Gln Ile Tyr Phe Leu Pro Glu Pro Gly Phe Ser Lys Glu Leu Ser Thr
20 25 30

Tyr Ser Val Phe Phe Thr Phe Tyr Ser Phe Leu Tyr Leu Thr Pro Ile
35 40 45

Trp Leu Leu His Ser Ser Leu Tyr Gln Lys Cys Leu Tyr Gly His His
50 55 60

Cys Pro Leu Cys Tyr Gln Ile Gln Thr Arg Leu Cys Pro Gln Leu Thr
65 70 75 80

Pro Pro Leu Asn Ser Leu Gln His Ser Leu Leu Ser Ser Pro Ser Asn
85 90 95

Ile Leu Leu Ser Leu Pro Ala Thr Tyr Thr Leu Arg Val Phe Leu Leu
100 105 110

Pro Leu Tyr His Leu Leu Ile Cys Trp Leu Phe Phe Phe Tyr Met Ile
115 120 125

Ser Lys Arg Gly Ile Leu Arg Ala Pro Phe Trp Val Leu Phe Ser Val
130 135 140

Trp Thr Val Pro Leu His Asp Phe Thr His Ser His Ala Phe Lys Cys
145 150 155 160

His Leu His Ala Asp Gly Ile Ile Cys Ile Ser Ser Leu Asp Val Ser
165 170 175

Ser Glu Phe Gln Ile Ser Ile Phe Asn Tyr Leu Leu Asp Ser His Cys
180 185 190

His Ile Gly Ile Leu Leu His Lys Gly Asp
195 200

BNSDOCID: <WO_ 0166751A2_I_>

<210> 177
<211> 120
<212> PRT
<213> Homo sapiens

<400> 177

Ala Ile Ser Ser Phe Ser Cys Cys Phe Phe Gly Ile Tyr Leu Phe Thr
1 5 10 15

Ser Gly Cys Phe Lys Asp Phe Phe Phe Leu Cys Cys Ile Phe Cys Pro
20 25 30

Ile Asp Trp Tyr Ser Ile Tyr Thr His Val Gly Ser Phe His Cys Pro
35 40 45

Thr Phe Leu Met Pro Leu Leu Tyr Phe Ser Thr Phe Cys Cys Gly Ser
50 55 60

Leu Tyr Phe Ser Val Leu Ser Phe Tyr Leu Pro Val Tyr Lys Pro Phe
65 70 75 80

Ile Leu Leu Val Asn Asp Ser His Glu Phe Leu Ile Ser Val Met Ile
85 90 95

Leu Leu Phe Ile Leu Gly Leu Phe Phe Phe Phe Phe Phe Phe Phe Ala
100 105 110

Cys Leu Phe Glu Met Glu Ser Arg
115 120

<210> 178
<211> 151
<212> PRT
<213> Homo sapiens

<400> 178

Arg Ser Met Cys Phe Leu Pro Asp Tyr Pro Ala Cys Ser Leu Gly Phe
1 5 10 15

His Leu Val Lys Leu His Thr Pro Gln Gly Val Cys Phe Ile Ser Ser
20 25 30

Val Leu Ser Lys Cys Leu Val His Ile Pro Val Val Ala Phe Ser Asn
35 40 45

Ser Pro Tyr Gly Ile Leu Ile Phe Thr Leu Leu Val Cys Val Ser Tyr
50 55 60

Trp Thr Leu Ser Lys Val Gly Ser Val Leu Arg Arg Lys Leu Gly Leu
65 70 75 80

His Gln Gly Lys Val Asn Leu Leu Val Ile Arg Leu Val His Glu Tyr
85 90 95

Asn Gly Ile Gly Ser Gly Arg Arg Glu Gln Cys Ala Met Ile Val Pro
100 105 110

Gln Thr Thr His Asp Cys Gly His Gly Ser Pro Leu Ile Thr Leu Pro
115 120 125

Gln Val Ser Thr Leu Ile Arg Glu Thr Asn Trp Glu Lys Val Gly Ser
130 135 140

BNSDOCID <WO__0166751A2_I_>

Trp Ala Glu Gly Ile Trp His
145 150

<210> 179
<211> 207
<212> PRT
<213> Homo sapiens

<400> 179

Phe Ile Phe Leu Leu Ser Asn Ser Ile Ile Cys Ser Ser Thr Phe Arg
1 5 10 15

Tyr Val Gln Thr Asp Ile Leu Tyr Ser Leu His Cys Lys Ser Phe Gln
20 25 30

Phe Ser Lys Tyr Pro Phe Trp Phe Cys Ala Phe Lys Ile His His Leu
35 40 45

Thr Ser Phe Cys Ser Ile Ser Glu Asn Phe Lys Ala Leu Phe Glu Ser
50 55 60

Arg Tyr His Met Thr Ala His Leu Arg Glu Ser Thr Leu Met Pro Leu
65 70 75 80

Ile Ser Leu Lys Tyr Ser Ile His Lys Tyr Phe Arg Asn Leu Val Ile
85 90 95

Glu Ile Leu Leu Lys Phe Ile Leu Tyr Ala Leu Thr Ser Leu Ile Ser
100 105 110

Met Thr His Cys Asn Tyr Leu Leu Ala Leu Lys Leu Gln His Asn Lys
115 120 125

Thr Tyr Ile Tyr Lys Leu Glu Leu Arg Thr Glu Thr Lys Asn Gln Ser
130 135 140

Lys Ile Thr Ser Val Ile Ile Phe Leu Thr Ile Ala Ser Gln Phe Phe
145 150 155 160

Thr Ile Val Val Phe Arg Leu Thr Thr Ser Phe His Asn Ala Glu Phe
165 170 175

Tyr Phe Leu Asn Ala Gln Ile Ser Glu Met Ile Phe Ile Tyr Phe Leu
180 185 190

Ser Phe Met Gly Ala Ser Val Val Leu Gly Ser Glu Phe Lys Cys
195 200 205

<210> 180
<211> 211
<212> PRT
<213> Homo sapiens

<400> 180

Ile Phe Leu Phe Ala Leu Ala Ser Pro Pro Val Ser Tyr Leu Leu Pro
1 5 10 15

Cys Leu Ser Met Gly Thr Leu Gly Asp Ala Pro Val Phe Cys Gly Arg
20 25 30

Thr Phe Lys Phe Pro Val Gln Thr Pro Asp Tyr Asn Tyr Ser Leu Gln
35 40 45

ENSDOCID <WO 0166751A2_I_>

Thr Ala Cys Val Leu Leu Asp Phe Leu Gly Phe Leu Ile Ile Leu Ile
50 55 60

Ser Gln Lys Ser Leu Ile Lys Thr Ser Tyr Thr Phe Ile Tyr Leu Lys
65 70 75 80

Asn Asn Leu Arg Leu Arg Val Glu Gly Gln Lys Leu Arg Lys Glu Arg
85 90 95

Ile Ser Ser Cys Asn Cys Ser Ile Leu Lys Val Lys Ala Ser Ile Tyr
100 105 110

Ile Leu Cys Trp Phe Pro Phe Val Leu Ile Leu Gly Ile Leu Ser Asn
115 120 125

Cys His Leu Leu Cys Lys Tyr Leu Leu His Val Pro Leu Asn Phe Ile
130 135 140

Ser Gly Ile Phe Arg Asp Thr Asp Val Leu His Phe Asn Ala Asp Lys
145 150 155 160

Ser Val His Phe Ser Leu Asp Phe Trp Leu Val Gly His Ala His Glu
165 170 175

Ala Phe Leu Leu His Asn Phe Lys Ser Phe Leu Asp Tyr Leu Leu Lys
180 185 190

Phe His Gly Ser Leu Phe His Ile Ile Phe His Gly Gln Ile Ile Tyr
195 200 205

Glu Asp Phe
210

<210> 181
<211> 202
<212> PRT
<213> Homo sapiens

<400> 181

Gln Asn Ser Trp Cys His Pro Leu Pro Ser Phe Ser Pro Ile His Ile
1 5 10 15

Ser Thr Arg Lys Gln Val Arg Phe Lys Thr Asn Cys Phe Ser His Leu
20 25 30

His Phe Cys Cys Pro Asp Leu Ser His His His Leu Asn Tyr Tyr Lys
35 40 45

Ser Gln Val Ser Val His Val Thr Pro Leu Leu Lys Ser Leu His Ser
50 55 60

Phe Pro His His Ser Glu Ser Leu Ala Gln Pro Phe Arg Arg Pro His
65 70 75 80

Ala Ile Pro Gly Phe Ser Ala Ser Thr Leu Ala Arg Val Gly Ser Cys
85 90 95

Thr Gln Ala Gly Phe Phe Ala Leu Pro His Thr Ser Ala Leu Pro Phe
100 105 110

Ser Gly Pro Leu His Leu Phe Pro Leu Cys Gly Thr Pro Ser Pro Arg
115 120 125

BNSDOCID: <WO__0166751A2_I_>

```
Cys Ala Pro Ala Ser Gln Ser Thr Phe Ser Pro Ser Ser Ser Leu Leu
    130                 135                 140

Arg Tyr His Leu Leu Ser Gly Thr Leu Phe Thr Ile Pro Ala Ser Leu
145                 150                 155                 160

Pro Ser Thr Ser Val Leu Phe Val Cys Phe Phe Ile Thr Leu Tyr Pro
                165                 170                 175

Phe Tyr Ser Arg His Tyr Trp Glu Tyr Leu Leu Phe Val Val Cys Leu
            180                 185                 190

Thr Cys His Val Met Ser Thr Arg Gln Gly
        195                 200
```

<210> 182
<211> 203
<212> PRT
<213> Homo sapiens

<400> 182

```
Ser Leu Lys Leu Trp Phe Thr Ile Tyr Gln Glu Gln Asn Val Ser Ile
1               5                   10                  15

Lys Thr Leu Glu Gly Ile Lys Tyr Asn Gly Asn Ser Leu Ile Met Ser
            20                  25                  30

Cys Phe Asn Glu Asn Glu Leu Val Leu Lys Ser Phe Lys His Lys Gly
        35                  40                  45

Lys Cys Val Thr Asn Met Lys Ser Cys Met Phe Ile Cys Phe Thr Met
    50                  55                  60

Val Gln Phe Leu Leu Cys Ile Cys Ile Pro His His Phe Val Cys Leu
65                  70                  75                  80

Gln Tyr Thr Lys Asn Leu Phe Lys Met Asn Ile Ala Leu Met Arg Lys
                85                  90                  95

Asp Leu His Lys Leu Val Ser Thr Val Met Thr Phe Met Ala Pro Ser
            100                 105                 110

Phe Arg Phe Val Leu Asn Phe Pro His Asn Pro Ser Val Thr Ile Ile
        115                 120                 125

Ser Asn Phe Ser Tyr Phe Thr Phe Gln Leu Phe His Asn Cys Thr Ile
    130                 135                 140

Leu Lys Pro Leu Thr Asn Val Ser Thr Lys Thr Thr His Thr His Thr
145                 150                 155                 160

Gln Asn Arg Leu His Ser Gln Trp Phe Ile Asp Tyr Cys Leu Gln Ala
                165                 170                 175

Leu Glu Asn Thr Tyr Met Tyr Ser Ala Leu Cys Ser Cys Ser Glu Ser
            180                 185                 190

Leu Leu Leu Pro Arg Ser Ser Cys Lys Asn Ser
        195                 200
```

<210> 183
<211> 184
<212> PRT
<213> Homo sapiens

BNSDOCID <WO_ 0166751A2_>

<400> 183

Gln Ala Leu Phe Leu Leu Val Ala Ser Leu Ser Gln Met Ser Ser Leu
1 5 10 15

Ser Leu Asp Ser Ser Ser Gln Cys Pro Pro Leu Thr Ala His Arg Leu
20 25 30

Ser Ser His Ser Ser Ile Leu Arg Val Asn Ser Ser Ser Glu Lys Pro
35 40 45

Ile Ser Trp Pro Leu Leu Ser Thr His Asn Thr Gly Phe Arg Val Phe
50 55 60

Leu Gln Thr Leu Ile Thr Ile His Ser Tyr Lys Phe Thr Ser Ala Ser
65 70 75 80

Pro Pro Pro Asn Gln Ala Leu Val Cys Leu Ala His Tyr Ser Ala Ile
85 90 95

Ser Ala Asn Ser Ala His Ala Met Gly Leu His Lys Cys Cys Met Asp
100 105 110

Glu Ile Leu Pro Tyr Met Tyr Phe Tyr Arg Trp His Thr Phe Ile Phe
115 120 125

Leu Pro Tyr Asn Cys Ile Ala Ile Cys Tyr Ile Asn Val Tyr Ser Pro
130 135 140

Val Arg Ala Val Val Leu Asn Ser Lys Cys Arg Arg Lys Glu Ser Pro
145 150 155 160

Ala Gly Asp Leu Leu Arg Val Pro Leu Pro Gly Ser Arg Asp Ala Ala
165 170 175

Leu Ser Ser Leu Gly Trp Asp Pro
180

<210> 184
<211> 167
<212> PRT
<213> Homo sapiens

<400> 184

Ile Ile Leu Leu Arg Cys Ile Phe Leu Tyr Phe Pro Leu Pro Val Ala
1 5 10 15

Lys Arg His Ile Leu Gln Lys Ser Gly Pro Tyr Ile Ser Ser Glu Val
20 25 30

Phe Ala Leu Leu Ser Leu Trp Thr Ile Ile Gln Val Ile Gly Asp Ser
35 40 45

Trp Pro Ser Gln Glu Gly Arg Leu Pro His Asn Gln Gly Leu Gly Leu
50 55 60

Thr Pro Cys Thr Ser Cys Ile Asn Lys Leu Cys Leu Ile Gln Ala Pro
65 70 75 80

Arg Gln Thr Gln Asn Lys Arg Tyr Pro Gln Arg Ala Ala Gly Arg Lys
85 90 95

Leu Val Cys Tyr Leu Gly Gly Gly Gln Lys Leu Lys Leu Arg Thr Lys

BNSDOCID <WO 0166751A2 I >

```
            100                 105                 110

Leu Ala Trp Leu Ile Leu Leu Asp Asn Pro Cys Pro Pro Pro Pro Gly
        115                 120                 125

Pro Thr Ser Leu Ser Leu Ser Leu Ser Leu Cys Leu Ser His Thr His
    130                 135                 140

Thr His Thr His Thr His Thr His Thr His Thr His Thr Phe Leu Ile
145                 150                 155                 160

Ala Gln Pro Arg Lys Val Gln
                165
```

<210> 185
<211> 207
<212> PRT
<213> Homo sapiens

<400> 185

```
Ser His Leu Phe Ser Phe Glu Ser Leu Ser Leu Thr His Leu Glu Val
1               5                   10                  15

Cys Cys Ser Ala Phe Ile Ser Thr Lys Thr Ser Ile Ile Ile Met Arg
            20                  25                  30

Tyr Leu Thr Val His Val Thr Val Ser Phe Trp Ile Tyr Phe Thr Ser
        35                  40                  45

Thr Asn Val Phe Phe Asp Cys Thr Leu Ser Thr Tyr Phe Gln Thr His
    50                  55                  60

Ile Leu Lys Ser Ser Gly Pro Arg Lys Ala Pro Pro Lys Lys Ser Tyr
65                  70                  75                  80

Arg Thr Ile Phe Thr Val Ala Ser Leu Val Asn Pro Phe Leu Ile Thr
                85                  90                  95

Ser Phe Ser Leu Phe Leu Leu Phe Val Val Ile Gln Val Tyr Asn Leu
            100                 105                 110

Leu Ile Phe Leu Ile Pro Ser Phe Tyr Lys Pro Leu Leu Ser Ser Ser
        115                 120                 125

Ser Leu Leu Trp Asn His Arg Leu Asp Cys Leu Asn Phe Phe Ser Tyr
    130                 135                 140

Pro Val Ala Leu Ile Cys Cys His Ile Cys Ile Gly Tyr His Ile Cys
145                 150                 155                 160

Gln Ala Asn Asn Ser Ile Gln Ser Thr Thr Phe Ser Asp Cys Tyr Leu
                165                 170                 175

Leu Leu Glu Lys Lys Asn Leu Lys Pro Ser Ile Leu Thr His Leu Asn
            180                 185                 190

Pro Tyr Cys Pro Lys Leu Ser Gly Leu Cys Ile Leu Ser Leu Leu
        195                 200                 205
```

<210> 186
<211> 172
<212> PRT
<213> Homo sapiens

ENSDOCID <WO 0166751A2 I >

<400> 186

Thr Phe Pro Pro Tyr Lys Ala Ile Ser Ile Ile Ile Trp Lys Phe His
1 5 10 15

Phe Thr Glu Ala Asn Gly Asn Phe Pro Val Thr Gln Lys Ala Leu Glu
20 25 30

Thr Val Ser Asn Cys Pro Ala Gly Pro Phe Leu Phe Ala Gly Ile Trp
35 40 45

Asp Phe Lys Gln Ser Leu Cys Leu Asn Arg Gly Gly Cys Lys His Ala
50 55 60

Cys Lys Phe Ser Gln Leu Pro Phe Trp Gly Leu Lys Ile Tyr Leu Phe
65 70 75 80

Ala Val Ser Gly Asn Ile Phe Leu Ser Trp Val Pro Cys Phe Met Pro
85 90 95

Leu Ile Tyr Arg Ser Phe Ser Thr Asn Lys Tyr Lys Leu Thr Val Arg
100 105 110

Ser Gln Pro Phe Gly Glu Leu Ser Lys Ser Leu Gln Glu Gly Arg Thr
115 120 125

Gly Thr Ile Phe Gly Lys Ser Gln Leu Phe Tyr His Phe Pro Gly Gly
130 135 140

Asp Ala Asp Trp Ile Leu Ala Pro His Arg His Pro Met Arg Gln Thr
145 150 155 160

Gly Leu His Leu Leu Ser Ala Tyr Arg Glu Arg Arg
165 170

<210> 187
<211> 213
<212> PRT
<213> Homo sapiens

<400> 187

Val Phe Asn Ile Ser His Phe Ser Leu Met Leu Phe Val Glu Leu Cys
1 5 10 15

Ser Lys Leu Ser His Lys Pro Val Leu Leu Leu Arg Gly Val Val Leu
20 25 30

Thr Val Val Ala Cys Ser Gln Asn Ser Lys Arg Leu Val Met Ala Lys
35 40 45

Val Asn Phe Asn Asn Asn Asn Asn Asn Asn Asn Asn Pro Trp Lys Lys
50 55 60

Asn Thr Arg Tyr Pro Glu Arg Asp Gln Leu Leu Gly Ile Leu Asn Gly
65 70 75 80

Lys Cys Phe Ile Trp Gly Lys Leu Leu Phe Asn Ser Phe Leu Val Lys
85 90 95

Trp Gln Ser Pro Ala Lys Leu Leu Ser Gln Gly Asp His Pro Gly Arg
100 105 110

Ser Arg Trp Asp Leu Pro Ser Gly Val Phe Gln Met Arg Leu Ser Phe
115 120 125

BNSDOCID <WO 0166751A2>

```
Glu Arg Pro Pro Gly Asp Ser Met Pro Pro Pro Ala Asp Leu Leu Ile
    130                 135                 140

Ser Thr Pro Ala Ala Leu Asn Pro Cys Thr Arg Gln Asp Val Leu Ser
145                 150                 155                 160

Ile Ser Pro Trp Pro Ser Gly Phe Pro Ala Ser Ala Val Gln Ser Ser
                165                 170                 175

Val Leu Ala Pro Phe Val Arg Arg Met Ser Tyr Pro Arg Leu Thr Ala
            180                 185                 190

Pro Cys Asp Leu Val Gly Glu Leu Ser Arg Thr Ala Val Thr Phe Ser
        195                 200                 205

Ile Phe Cys Tyr Met
    210
```

<210> 188
<211> 201
<212> PRT
<213> Homo sapiens

<400> 188

```
Cys Phe Asp Trp Ala Gly Ser Thr His Phe Asp Met Pro Arg Ser Trp
1               5                   10                  15

Leu Gln Gly Asp Thr Asp Ser Gly Asp Ser Arg Ala Leu Val Arg Ala
            20                  25                  30

Ala Thr Lys Glu Val Ala Asp Phe Leu Ile Ile Ile Gln Ala Gln Leu
        35                  40                  45

Leu Tyr Asn Leu Phe Leu Asn Tyr Tyr Thr Gly Gln Thr Arg Leu Pro
    50                  55                  60

Gly Tyr Pro Gly Leu Gly His Thr Ser Ile Val Phe Lys Leu Asn Val
65                  70                  75                  80

Phe Asn Leu Lys Thr Ser Asn Thr Phe Ser Met Lys Thr Glu Lys Arg
                85                  90                  95

Asp Lys Gln Lys Glu Lys Ile Ile Lys Tyr Ile Ile Leu Val Pro Ser
            100                 105                 110

Ser Asn His Cys Tyr His Tyr Gly Val Ile Ile Leu Val Val Cys Thr
        115                 120                 125

Phe Phe His Met Tyr Leu Gly Val Met Gly Lys Cys His Pro Arg Arg
    130                 135                 140

Leu Ile Thr Cys Phe Pro Tyr Leu Tyr Ser Phe Val Cys Val Thr Phe
145                 150                 155                 160

Trp Ile Thr Leu Ser Arg Gly Glu Val Asn Asn Ser Cys Arg Tyr Thr
                165                 170                 175

Asn Gln Ser Ser Glu Gly Lys His Gln Val Arg Phe Thr Asp Asp Ser
            180                 185                 190

Cys Ile Cys Thr Gln Phe Thr Cys Lys
        195                 200
```


ENSDOCID <WO___0166751A2_I>

<210> 189
<211> 129
<212> PRT
<213> Homo sapiens

<400> 189

Val Gln Lys Ala Met Phe Lys Leu Asn Tyr Ala Ile Asp Thr Tyr Cys
1 5 10 15

Met Glu Pro Thr Leu Ile Leu Lys Gln Lys Glu Trp Asn Val Gly Glu
20 25 30

Gln Ala Cys Phe Leu Ile Glu His Thr Asn Asn Leu Lys Glu Ile Phe
35 40 45

Val Leu Gln Lys Lys His Thr Arg Ser Ile Thr Arg Cys Leu Pro Val
50 55 60

Phe Lys Pro Arg Gln Ser Lys Asn His Arg Cys Leu Leu Lys Lys Cys
65 70 75 80

Ser Arg Trp Arg Val Ser Ser Lys Ala Val Thr Ser Ser Tyr Ser Tyr
85 90 95

Leu Tyr Arg Cys Met Ile Ile Ile Gly Asp Tyr Leu Asn Phe Phe Arg
100 105 110

Val Pro Met Ile Ile Asp Asn Phe Ile Val Ile His Ile Val Val Leu
115 120 125

Gly

<210> 190
<211> 211
<212> PRT
<213> Homo sapiens

<400> 190

Thr Arg Thr Leu Thr Asp Gly Trp Arg Trp Pro Gly Gln Leu Cys Trp
1 5 10 15

Gly His Thr Phe Gly Ile Leu Val Pro Thr Val Gly Trp Val Pro Trp
20 25 30

Val Phe Cys Met Ser Phe Leu Leu Arg Trp Asn Val Gln Lys Gly Ser
35 40 45

Phe Thr His Met Pro Gly Trp Asp Arg Gln Ser Ser Gln Gly Trp Pro
50 55 60

Asp Thr Phe Leu Ser Ser Asp Gly Val Ser Met Trp Val Pro Gly Leu
65 70 75 80

Pro His His Val Ser Asp Thr Cys Tyr Ile Val Ser Gly Phe Cys Gln
85 90 95

Ser Gln His Ser Lys Arg Leu Gln Glu Ala Ser Tyr Asn Ser Ala Ser
100 105 110

Arg Val Pro Glu Cys His Leu Cys His Ile Arg Trp Ile Thr Gln Val
115 120 125

BNSDOCID <WO 0166751A2_I_>

```
Thr Gly Arg Pro Val Cys Glu Arg Leu Gly Ile Arg Leu His Phe Pro
    130                 135                 140

Ser Gly Gly Glu Ala Thr Phe Asn Leu Leu Gln Lys Val Pro Phe Gln
145                 150                 155                 160

Cys Pro Ser Ile Leu Ile Arg Ser Val Lys Val Gln Pro Asn Val Leu
                165                 170                 175

Phe Glu Tyr Leu Ile Cys Cys Ser Asn Val Pro Asn Ser Arg Asp Phe
            180                 185                 190

His Arg Ser Pro Asn Pro Arg Thr Met Lys Thr Cys Leu Ser Lys Leu
        195                 200                 205

Ile Ala Met
    210
```

<210> 191
<211> 165
<212> PRT
<213> Homo sapiens

<400> 191

```
Leu Leu Tyr Arg Pro Asp Gln Ala Ser Trp Val Pro Arg Pro Val Arg
1               5                   10                  15

Pro His Ser Ile Val Phe Lys Leu Asn Val Phe Asn Leu Lys Thr Ser
            20                  25                  30

Asn Thr Phe Ser Met Lys Thr Glu Lys Arg Asp Lys Gln Lys Glu Lys
        35                  40                  45

Ile Ile Lys Tyr Ile Ile Leu Val Pro Ser Ser Asn His Cys Tyr His
    50                  55                  60

Tyr Gly Val Ile Ile Leu Val Val Cys Thr Phe Phe His Met Tyr Leu
65                  70                  75                  80

Gly Val Met Gly Lys Cys His Pro Arg Arg Leu Ile Thr Cys Phe Pro
                85                  90                  95

Tyr Leu Tyr Ser Phe Val Cys Val Thr Phe Trp Ile Thr Leu Ser Arg
            100                 105                 110

Gly Glu Val Asn Asn Ser Cys Arg Tyr Thr Asn Gln Ser Ser Glu Gly
        115                 120                 125

Lys His Gln Val Arg Phe Thr Asp Asp Ser Cys Ile Cys Thr Gln Phe
    130                 135                 140

Thr Cys Gly Ala Gly Lys Glu Phe Ile Ser Trp Gly Asp Ala Phe Lys
145                 150                 155                 160

Thr Ile Thr Glu Phe
                165
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<210> 192
<211> 154
<212> PRT
<213> Homo sapiens

<400> 192

ENSDOCID <WO 0166751A2 >

Ile Ile Leu Ser Leu Pro Pro Pro Ser Pro Pro Lys Arg Leu Thr Cys
1 5 10 15

Asp Ser Trp Ser Ala Arg Ser Asn Ala Phe Pro Ala Gly Ala Pro Gly
20 25 30

Gly Gln Gly Asp Val Pro Ser Phe Leu Cys Ala Thr His Pro His Phe
35 40 45

Ser Thr Pro Cys Gln Cys Trp Thr Gln Leu Asp Glu Asp Ser Leu Thr
50 55 60

Ala Asp Val Leu Ser Asn Ser Ile Lys Leu Gly Arg Phe Ser Cys Arg
65 70 75 80

Asn Pro Ile Cys Cys Gln Phe Glu Gly Gly Lys Gln Phe Gln Leu Arg
85 90 95

Lys Val Thr Gln Gly Lys Gly Val Lys Gly Ala Arg Leu Leu Gly Gly
100 105 110

His His Ile Ser Ile Trp Cys Phe Ile Ser Ala Asn Ser Leu Leu Val
115 120 125

Tyr Pro Glu Val Ile Ser Leu Tyr Arg Ser Ser His Ile Ala Lys Leu
130 135 140

Thr Lys Ile Asp Arg Asp Lys His Arg Lys
145 150

<210> 193
<211> 154
<212> PRT
<213> Homo sapiens

<400> 193

Lys Val Ala Asn Leu Cys Lys Arg His Glu Ile Arg Asn Ile Ile Lys
1 5 10 15

Lys Met Ile Phe Ile Ala Lys Ala Pro Ala Ser Thr Thr Val Ile Ser
20 25 30

Leu Tyr Gln Phe Ala Gln Arg Ser His His Ile Phe Ser Gly Thr His
35 40 45

Pro Leu Tyr Phe Cys Ala Ser Leu Phe Ile Ile Ser Gln Ser His Arg
50 55 60

Ser Ser Lys Val Asn Leu Pro Asp Lys Ile Val Phe Leu Leu Val Leu
65 70 75 80

Ser Asn Phe Leu Val Ile Tyr Asp Tyr Val Thr Lys Tyr Leu Lys Phe
85 90 95

Ser Cys Leu Asn Lys Gln Thr Phe Tyr Phe Ile Thr Trp Phe Cys Glu
100 105 110

His His Leu Gln Leu Ser Leu Ser Ile Tyr Leu Ile Cys Glu Ala Leu
115 120 125

Thr Gly Val Thr Val Cys Tyr Ser Ala Ser Cys Leu Arg Leu Ser Arg
130 135 140

Glu Thr Ile Ile Ser Leu Pro Ala Ile Ala

BNSDOCID <WO_ 0166751A2_I_>

145 150

<210> 194
<211> 172
<212> PRT
<213> Homo sapiens

<400> 194

Ile Phe Thr Glu Ile Phe Lys Val Asn Leu Asp Arg Ser Leu Tyr Pro
1 5 10 15

Phe Lys Cys Phe Ser Val Lys Leu Tyr Leu Ile Gln Ile Leu Tyr Pro
20 25 30

Val Asp Cys Arg Leu Ile Tyr Phe Asn Glu His Leu Leu Asn Arg Thr
35 40 45

Met His Glu Tyr Ile Ser Glu Gly His Gly Leu Thr Leu Glu Tyr Val
50 55 60

Ala Phe Pro Phe Ser Tyr Asn Ile Cys Arg Leu Arg Leu Ser Ile Ile
65 70 75 80

Asp Leu Leu Lys Phe Ser Ile Phe Asn Ala Ile Asn Asp Leu Asp Met
85 90 95

Val Lys Leu Val Phe Ile His Phe Ser Ala Lys Ile Ser Asp Gly Ser
100 105 110

Val Val Ser Gly Asn Gln Glu Leu His Ile Phe Tyr Tyr Phe Tyr Arg
115 120 125

Met Ile Phe Ser Ile Lys Asn Leu Gln Leu Ile Ile Ala Leu Arg Arg
130 135 140

Ile Ala Phe His Phe Glu Thr Lys Ser Gln Val Met Asp Phe His Phe
145 150 155 160

Leu Gly Leu Tyr Ser Asn Met His Cys Leu Leu Ser
165 170

<210> 195
<211> 85
<212> PRT
<213> Homo sapiens

<400> 195

Pro Val Gly Ala Asn Gly Leu Asn Gly Arg Asn Ala Thr Ala Pro Arg
1 5 10 15

Ser Leu Ala Ile Val Leu Gln Pro Glu Asn Leu Phe Tyr Lys Leu Gly
20 25 30

Asn Ser Ile Cys Gly Glu Glu Arg Glu Ser Leu Pro Pro Arg Pro Gln
35 40 45

Glu Met Ala Gly Lys Glu Thr Ile Lys Arg Leu Ser Arg Leu Trp Gly
50 55 60

Phe Val Val Gly Pro Thr Arg Ala Ile Ser Gly Lys His Ser Ala Arg
65 70 75 80

Leu Phe Thr Ser Gln

ENSDOCID <WO 0166751A2_I >

85

<210> 196
<211> 185
<212> PRT
<213> Homo sapiens

<400> 196

Ala Ser Phe Phe Ala Phe Phe Phe Asp Gly Gly Thr Leu Ile Val Phe
1 5 10 15

Ser Phe Lys Leu Lys Asn Asn Thr Arg Tyr Ile Ile Met Ser Leu Leu
20 25 30

Ile Lys Leu Leu Asp Ser Ile Tyr Leu Leu Pro Thr Ile Lys Arg Arg
35 40 45

Val Arg His Leu Phe Leu Leu Pro Lys Asn Thr Leu Asn His Pro Asn
50 55 60

Asn Tyr Phe Ser Tyr Asn Thr Gly Leu Tyr Tyr Tyr Leu Ile Leu Cys
65 70 75 80

Asp Asp Lys Leu His Ser Cys Leu Ala Leu Phe Leu Phe Leu Ser Gly
85 90 95

Leu Arg Val His Cys His Ser Pro Thr Pro Phe Gln Leu Ser Ala Ile
100 105 110

Phe His Phe Leu Phe Gly Cys Ile Leu Ser Tyr Leu Gln Gly Phe Ser
115 120 125

Phe Gln Glu Ile Ser Trp Ser Leu Tyr Ser Ser Ser Leu Tyr Lys Trp
130 135 140

Asn Arg Ser Val Ala Val Ile Tyr Gln Gln Gln Ser Asn Asn Ser Ala
145 150 155 160

Met Ser Leu Gly His Thr Thr Phe Ser Pro Ser Gly Pro Ile Gly Thr
165 170 175

Ala Leu Leu Ser Ser Gly Ser Asp Cys
180 185

<210> 197
<211> 188
<212> PRT
<213> Homo sapiens

<400> 197

Ser Pro Val Ala Val Leu Leu Lys Cys Ile Pro Ser Val Ser Ala Thr
1 5 10 15

Phe Ala Gln Ile Pro Ala Ser Gly Ser Ala Ser Gly Ser Leu Thr Gly
20 25 30

Gly Ser Thr Val Arg Glu Pro Leu Trp Phe Lys Val Ser Gln Thr Asp
35 40 45

Tyr Arg Ala Gln Arg Tyr Pro Leu Ala Asn Glu Asn Leu Pro Thr Glu
50 55 60

Lys Lys Pro Met Leu Gln Ile Cys Glu Gln Ile Ala Lys Tyr Glu Glu

BNSDOCID: <WO 0166751A2 >

65 70 75 80

Gly Asn Ile Thr Phe Thr Asn Phe His Lys Gly Arg Asp Ser Gln Asn
85 90 95

Thr Ser Tyr Arg Tyr Cys Val Asn Arg Leu Trp Ile Ser Phe Leu Gly
100 105 110

Leu Leu Gln Ile Thr Lys Thr Trp Leu His Lys Ala Ile Asp Leu Tyr
115 120 125

Trp Leu Ile Val Leu Glu Ala Arg Ser Thr Lys Ser Arg Cys Arg Gln
130 135 140

Val Asn Ser Phe Cys Lys Leu Cys Gly Arg Ile Cys Ser Leu Pro Leu
145 150 155 160

Ser Ser Leu Leu Gly Leu Pro Gln Ser Ser Val His Leu Asp Phe Arg
165 170 175

Cys Ile Ala Ala Ala Val Pro Pro Pro Ser Ser Lys
180 185

<210> 198
<211> 228
<212> PRT
<213> Homo sapiens

<400> 198

Gln Ser Arg Arg Asp Gly Lys Val Tyr Phe Trp Pro Asp Cys Ile Ala
1 5 10 15

Ser Cys Leu Thr Pro Pro Ala Gln Leu Ala Phe Arg Trp Ala Leu Pro
20 25 30

Ala His Gly Lys Ser Arg Arg Lys Trp Lys Arg Arg Phe Phe Arg Asn
35 40 45

Gln His Thr Ile Gln Arg Leu Ser Phe Phe Pro Ser Leu Arg Glu Lys
50 55 60

Glu Arg Glu Arg Glu Ser Ser Arg Gln Val Asn Phe Thr Gly Ala Glu
65 70 75 80

Tyr Leu His Gln Ser Glu Pro Gly Leu Glu Asn Cys Ser Pro Gln Ala
85 90 95

Pro Trp Val Gly Lys Glu Glu Ala Ala Ala Ala Leu Lys Ser Pro Thr
100 105 110

Gln Leu Cys Phe Ile Gly Pro Glu Ser Ala Lys Thr Ser Asp Val Pro
115 120 125

Asn Ile Arg Gln Pro Ser Arg Pro Met Leu Ala Pro Lys His Asn Gln
130 135 140

Lys Pro Lys Arg Ser Val Ser Asn Val Pro Glu Cys Phe Tyr Ile Ser
145 150 155 160

Trp Thr Thr Ile Leu Leu Gly Asn Val Arg Arg Ala Val Cys Ser Met
165 170 175

Glu Ala Pro Glu Lys Ile Ile Ser His Ala Lys Ala Gly Ala Gly Gly
180 185 190

ENSDOCID <WO 0166751A2 >

Cys Phe Pro Leu Gly Asn Gly Val Gly Ser Ile Thr Leu Arg Gln Ala
195 200 205

Ile Lys Gln Ala Phe Lys His Ile Leu Cys Gly Ser Asn Ser Thr Ser
210 215 220

Gly Asp Arg Phe
225

<210> 199
<211> 165
<212> PRT
<213> Homo sapiens

<400> 199

Phe Ser Ser His Leu Glu Cys Gly His Asp Thr Phe Gln Tyr Val Phe
1 5 10 15

Tyr Ser Trp Lys Val Asn Thr His Phe Thr Ser Ile Val Leu Lys Ile
20 25 30

Asp Lys Met Cys Phe Cys Ser Glu Val Ile Thr Leu Leu Cys Ile His
35 40 45

Ile Tyr Leu Asn Tyr Leu Lys Met Glu Pro Val Glu Ser Glu Ile Glu
50 55 60

Leu Asn Gly Ile Ile Leu His Cys Val Leu Met Val Cys Ala Ser Asp
65 70 75 80

Met Met Ser His Leu Ile Thr Val His Thr Lys Trp Ile Lys Tyr Val
85 90 95

Asp Asn Ile Thr Cys Leu Asn Ile Lys Cys Gly Ile Lys Arg Leu Ser
100 105 110

Ser Ile Ala Ile Met Gln Asn Val Ile Ala Phe Arg Glu Tyr Leu Trp
115 120 125

Asp Glu Ile Gly Asn Leu Ile Glu Thr Thr Ile His Ile Asn Val Ser
130 135 140

Tyr Thr Phe Glu His Ser Lys Ala Ser Gln Phe Gly Asn Asn Leu Val
145 150 155 160

Ser Leu Val Thr Glu
165

<210> 200
<211> 109
<212> PRT
<213> Homo sapiens

<400> 200

Pro Gly Glu Lys Val Gly Pro Glu Ser Ala Asp Leu Leu Glu Val Tyr
1 5 10 15

Leu Leu His Leu Pro Leu Ser Asn Leu Leu Val Thr Leu Pro Pro Gly
20 25 30

Phe Trp Gly Pro Tyr Ala Ala Leu His Gln Ala Pro Pro Val Leu Arg
35 40 45

BNSDOCID <WO 0166751A2 I >

Met Asn Trp Gly Glu Thr Phe Leu Lys Gly Tyr Leu Leu Thr Leu Tyr
50 55 60

Leu Gln Leu Thr Glu Leu Leu Thr Met Trp Arg Glu Asn Leu Gly Leu
65 70 75 80

Glu Thr Ile Gln Gly Arg Trp Gly Val Leu Gly Ile Ser His Ala Gly
85 90 95

Glu Ala Pro Leu Thr Pro Trp Gly Ser Lys Gly His Phe
100 105

<210> 201
<211> 203
<212> PRT
<213> Homo sapiens

<400> 201

Asp Ile Ser Leu Asn Val Glu Gln Arg Lys Leu Tyr Val Glu Val Gln
1 5 10 15

Cys Tyr His Asn Asn Asn Asn Lys Lys Tyr Val Val Arg Thr Cys Val
20 25 30

Ile Ser Ile Thr Leu Gly Glu Asp Leu Arg Gln Ser Leu Gly Lys Lys
35 40 45

Ser Ser Thr Asp Met Ala Ser Val Lys Val His Leu Leu Leu Lys Cys
50 55 60

Cys Arg Asp Met Lys Glu Ile Leu Val Leu Lys Leu Val Gln Leu Val
65 70 75 80

His Gln Val Ser Gln Asp Leu Glu Ile Asp His Ser Ala Leu Met Leu
85 90 95

Phe His Phe His Val Cys Leu Phe Thr Val Pro Glu Leu Cys Val Cys
100 105 110

Leu Leu Leu Leu Tyr Arg Ile His Ser Leu Lys Arg Asp His Leu Asp
115 120 125

Leu Phe Thr Ser Asn Thr Ile Trp Gly Phe Ser Ile Cys Ile Asn Leu
130 135 140

Arg Gly Thr His Ala Val Phe Leu His Arg Tyr Asn Ala Glu Trp Arg
145 150 155 160

Ser Leu Cys Leu Tyr Cys Asn His Tyr Leu Asn Asn Val His Cys Thr
165 170 175

His Val Asn Ser His Pro Ser Asn Pro Leu Pro Pro Ser His Pro Pro
180 185 190

Ser Phe Leu Ala Ser Asn Val Tyr Tyr Ser Thr
195 200

<210> 202
<211> 183
<212> PRT
<213> Homo sapiens

<400> 202

BNSDOCID <WO 0166751A2_I_>

Pro Leu Val Leu Leu Leu Val Phe Gln Tyr Phe Leu Cys Thr Cys Lys
1 5 10 15

Pro Lys Arg Cys His Ser Leu Arg Ile Ile Ser Leu Phe Thr Pro Leu
20 25 30

Leu Leu Ala Asn Phe Cys Pro Ser Phe Lys Met His Pro Lys His His
35 40 45

Leu Phe Ser Glu Asp Phe Pro Ile Pro Gln Ile Thr Lys Ala Leu Ser
50 55 60

Phe His Ser Ser Phe Leu Asn Gly His Lys Leu Ile Leu Gln Ser Ser
65 70 75 80

His Lys Leu Asp Ser Met Pro Leu Pro Leu Ala Pro Gly Trp Ala Gly
85 90 95

Cys Phe Thr Gln Ser Ile Ala Lys Val Ile Leu Val Phe Tyr Glu Ala
100 105 110

Glu Ser Glu Val Met Trp Leu Ser Pro Tyr Leu Leu Gly Tyr Thr His
115 120 125

Leu Glu Pro Glu Ala Ala Met Leu Gly Ser Leu Ala Leu Trp Gly Val
130 135 140

Met Cys Thr His Ser Thr Gln Gln Phe Cys Ser Leu Cys Leu Pro Ser
145 150 155 160

Trp Gly Pro Arg His His Glu Thr Glu Lys Ser His Leu Phe Ser Val
165 170 175

Ser Ser Val Pro Ser Pro Asn
180

<210> 203
<211> 149
<212> PRT
<213> Homo sapiens

<400> 203

Leu Leu Phe Ser Leu Pro Gly Met Leu Phe Leu Arg Ser Pro Gln Ala
1 5 10 15

Gln Leu Leu Leu Gly Leu Gln Val Leu Val Gln Arg Pro Leu Cys Ser
20 25 30

Leu Lys Pro Leu Gln Ala Ser His Gln Ile Thr Ser Ile Leu Trp Ala
35 40 45

Cys Phe Leu Phe Cys Ile Ala Phe Ile Thr Ile Ser Tyr Pro Ala Phe
50 55 60

Thr Tyr Leu Phe Ser Ser Phe Pro Thr Arg Met Thr Glu Gln Arg Leu
65 70 75 80

Leu Phe Ile Thr Val Ser Ala Glu Pro Ala Thr Met Val Ser Asn Lys
85 90 95

Thr Ile Asn Asn Cys Ser Met Asn Asp Cys Ser Leu Tyr Thr Gln Leu
100 105 110

ENSDOCID <WO 0166751A2_I >

Arg Glu Ile Lys Gly Lys Lys Asn Val Leu Tyr Thr Val Leu Ser Pro
115 120 125

Trp Ile Phe Thr Thr Leu Phe Gly Asn Arg Tyr Lys Thr Leu Thr Pro
130 135 140

Phe Asn Arg Glu Thr
145

<210> 204
<211> 146
<212> PRT
<213> Homo sapiens

<400> 204

Ile Lys Asp Val Asp Lys Ile Arg Leu Leu Leu Thr Phe Ala Thr Val
1 5 10 15

Arg Thr Cys Asn Leu Cys Tyr Ser Thr Tyr Asn Gly Lys Ser Leu Asp
20 25 30

Thr Phe Tyr Tyr Arg Asp Leu His Gly Leu Leu Leu Tyr Leu Ile Glu
35 40 45

Lys Lys His His Ser Gly Ile Cys Val Glu Thr Gly Pro Trp Arg Val
50 55 60

Arg Gly Gly Asn Trp Gly Ile Arg Glu Glu Asp Ile Ala Glu Val Phe
65 70 75 80

Ile Ala Glu Asp Gly Gly Leu Tyr Gly Lys Arg Ser Arg Asn Cys Glu
85 90 95

Lys Gly Pro Asp Leu Val Ser Glu Val Asn Val Val Asn Val Gly Ser
100 105 110

Glu Gly Arg Lys Asn Gly His Asn Asp Ser Tyr Ile Leu Ala Phe Val
115 120 125

Ser Arg Met Ser Gly Ala Val Arg Trp Arg Thr Leu Arg Val Ala Met
130 135 140

Gly Val
145

<210> 205
<211> 172
<212> PRT
<213> Homo sapiens

<400> 205

Trp Arg Leu Leu Pro Phe Glu Gly Ile Ser Phe Thr Phe Ala Leu Tyr
1 5 10 15

Asn Tyr Leu Phe Leu Leu Pro Leu Ser Leu Val Phe Ser Pro Ile Ser
20 25 30

Asp Ser Leu Cys Ser Leu Ser Gly Phe Arg Leu Cys Met Ser Arg Asn
35 40 45

Asn Arg Phe Thr Pro Ser Ala Gly Ile Gln Ala Leu His Phe Phe Cys
50 55 60

Cys Thr Phe Trp Glu Pro Tyr Tyr Leu Leu His Leu Thr Gln Ile Pro
65 70 75 80

Glu Ile Leu Leu Asn Ala Phe Val Lys Ile Ile Phe Leu Leu Thr Val
85 90 95

Thr Ile Thr Ser Leu Arg Tyr Gln Asp Asn Lys Ser Ser Met Leu Pro
100 105 110

Leu Thr Pro Ala Pro Val Ser Ala Gln Lys Pro Gln Arg Thr Trp Pro
115 120 125

Gln Ala Lys Tyr Gln Thr Asp Asn Tyr Ser Tyr Phe Ser Cys Lys Ser
130 135 140

Pro Phe Ser Ile Thr Thr Ser Ile Leu Lys Phe Leu Tyr Lys Ser Lys
145 150 155 160

Ile Ser Leu Lys Ile Ile Thr Phe Phe Phe Phe Leu
165 170

<210> 206
<211> 203
<212> PRT
<213> Homo sapiens

<400> 206

Arg Met Ile Asp Leu Leu Leu Leu Ser Thr Glu Ile Cys Trp Phe Met
1 5 10 15

Glu Arg Arg Met Arg Arg Thr Tyr Pro Pro Leu Thr Leu Gln Glu Gly
20 25 30

Lys Tyr Leu Glu Lys Pro Glu Thr Glu Thr Pro Lys Asp Leu Asn Ser
35 40 45

Leu Arg Ala Cys Ser Asp Ser Leu Ala Tyr Ala Thr Ser Gly Asn Arg
50 55 60

Ser Phe Phe Lys Ile Thr Cys Ala Asp Leu Val Thr Gln Gly Asp His
65 70 75 80

Thr Tyr Tyr Phe Leu Ser Ile Arg Asn Tyr Leu Trp Lys Gln Asp Asp
85 90 95

Phe Ile Ser Cys Leu Ala Leu Pro Leu Leu Phe Thr Glu Asn Gln Gln
100 105 110

His Ala Asn Asp Val Leu Lys Val Gln Ser His Leu Arg Thr Leu Gly
115 120 125

Ser Leu Ala Arg Glu Thr Leu Tyr Asp Thr Val Phe Lys Cys Thr Pro
130 135 140

Ile Gln Asn Cys Lys Tyr Leu Phe Cys Thr Asp Leu Ala Cys Thr Lys
145 150 155 160

Gln Pro Tyr Thr Val Tyr Ile Lys Cys Thr Ser Arg Leu Ser Ile Arg
165 170 175

Lys Arg Gly Lys His Pro Asn Tyr Ile Gln Arg His Tyr Trp Lys Leu
180 185 190

Ile Met Leu Ile Pro Ser Ile Met Gln His Leu

BNSDOCID <WO__0166751A2 |

195 200

<210> 207
<211> 182
<212> PRT
<213> Homo sapiens

<400> 207

Gln Tyr Phe Cys Ala Val Asn His Cys Phe Val Ser Ser Ala Tyr Leu
1 5 10 15

Lys Leu Asn Leu Asp Leu Leu Leu Met Ala Pro Asn Asn Thr Ser Ile
20 25 30

Ala Ile Ile Ser Lys Ile Glu Ile Asn Ile His Thr Trp Ser Met Ser
35 40 45

Val Leu Thr Cys Asn Ile Trp Leu Thr Gln Thr Met Ile Cys Cys Thr
50 55 60

Phe Tyr Asn Asp Gln His Cys Leu His Asn Tyr Lys Gln Met Leu Arg
65 70 75 80

Phe Tyr Lys Tyr Thr Cys Thr His Val Ser Ile Tyr Thr Cys Met Phe
85 90 95

Asn Ile Tyr Phe Cys Tyr Ala Ser Ile Cys Ile Val Trp Tyr Tyr Ser
100 105 110

Pro His Asn Arg Leu Met Lys Lys Val Tyr Ala Lys Leu Tyr Phe Ser
115 120 125

Phe Leu Lys Ile Ser Phe Ile Ile Leu Phe Cys Gly Gln Ile Leu Phe
130 135 140

Ile His Val Phe Ile His Ser Val Ile Ile Arg Thr Cys Ser Arg His
145 150 155 160

Ala Phe Lys Glu Lys Tyr Asp Ala Phe His Ile Phe Trp Glu Ile Ile
165 170 175

Val Ser Trp Glu Arg Ile
180

<210> 208
<211> 164
<212> PRT
<213> Homo sapiens

<400> 208

Val Gln Gly Glu Trp Met Glu Leu Val Glu Leu Asn Thr Cys Ile Tyr
1 5 10 15

Ser Leu Lys Leu Pro Asn Ser Ser Leu Pro Leu Ile Lys Gly Val Phe
20 25 30

Phe Leu Ile Gly Asn Ser Ile Ile Leu Tyr Glu Ile Gly Phe Phe Phe
35 40 45

Asn Val Trp Ile Leu Phe Gly Asp Val Leu Leu Ser Ser Ile Ser Val
50 55 60

Thr Gly Ser Trp Asn Phe Cys Asn Tyr Asn Cys Met Ser Phe Tyr Thr

ENSDOCID <WO 0166751A2 I

65 70 75 80

Phe Glu Asn Asn Ile Thr Ile Phe Asn Glu Ile Ile Ser Tyr Leu Glu
85 90 95

Ile Ile Ser Asn Lys Met Ser Pro Tyr Ala Val Val Ile Leu Gly Ala
100 105 110

Ser Phe Lys Met Lys Tyr Phe Val Ser Ile Thr Leu Pro Thr Tyr Pro
115 120 125

Phe Val Tyr Ala Phe Ala Asn Ile Asn Val Gln Met Phe Leu Tyr Ile
130 135 140

Leu Cys Cys Ile Ser His Ala Arg Ile Ser Phe Asn Ser Leu Tyr Asn
145 150 155 160

Tyr Phe Cys Pro

<210> 209
<211> 122
<212> PRT
<213> Homo sapiens

<400> 209

Phe Leu Gly Cys Lys Lys Pro Pro Thr Pro Phe Ser Phe Thr Leu Ser
1 5 10 15

Gly Gln Val Pro Leu Phe Trp Gly Arg Gly Lys Tyr Pro Asn Pro Leu
20 25 30

Tyr Leu Cys Ala Pro Ile Pro Asn Phe His Ala Pro Thr Ser Tyr Ile
35 40 45

Ser Ala Pro Gln Ser Leu Ile Ser Ala Pro Arg Pro His Ile Ser Val
50 55 60

Pro Pro Leu Ser Arg Leu Ser Gly Gly Glu Pro Pro Ser Pro Phe Pro
65 70 75 80

Ser Cys Leu Tyr Ser Leu Phe Ser Leu Gly Phe Thr Met Gly Asn Leu
85 90 95

Pro Pro Ser Ile Pro Pro Ser Ser Pro Leu Ala Cys Val Leu Lys Asn
100 105 110

Phe Trp Gly Ala Arg Asn Pro Gln Pro Leu
115 120

<210> 210
<211> 170
<212> PRT
<213> Homo sapiens

<400> 210

Thr Ile Leu Pro Asn Arg Ile Val His Val Tyr Cys Ile Val His Ile
1 5 10 15

His Thr Thr Tyr Phe Ile Ser Val Ser Leu Leu Val Leu Lys Asp Leu
20 25 30

Leu Thr Asp Gly Thr Lys Cys Ser Phe Leu Pro Phe Ala Tyr Cys Glu

BNSDOCID <WO_ 0166751A2_I_>

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        35                  40                  45

Glu Glu Thr Phe Ala Lys Ile Ser Gln Tyr Glu Asn Cys Ser Cys Phe
    50                  55                  60

Leu Lys Gly Lys Asn Glu Ser Leu Ser Phe Trp Ile Arg Asn Lys Phe
65                  70                  75                  80

Arg Met Ala Gln Lys Tyr Ile Asp Met Asn Tyr Leu Pro Glu Cys His
                85                  90                  95

Pro Met Leu Tyr Ile Phe Leu Gly Glu Asp Phe Trp Leu Phe Thr Ile
            100                 105                 110

Glu Ser Leu Val Thr Asn Val Leu Lys Leu Glu Ser Arg His Phe Arg
        115                 120                 125

Ser Ser Tyr Met Glu Leu Arg Lys Phe Lys Ala Ile Leu Met Lys Asn
    130                 135                 140

Phe Thr Met His Val Tyr Tyr Cys Ser Phe Ile Pro Asn Leu Ile Ile
145                 150                 155                 160

Val Lys Val Phe Val Ser Ser Thr Val Val
                165                 170
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<210> 211
<211> 229
<212> PRT
<213> Homo sapiens

<400> 211

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Trp Gln Gly Val Phe Pro Ser Pro Lys Arg His His Phe Glu Asn Tyr
1               5                   10                  15

Ile Val Met Trp Leu Lys Thr Ser Gln Leu Ser Ile Ile Gly Ala Ala
            20                  25                  30

Lys Tyr Phe Cys Asn Thr Leu Ala Asn Met Asn Trp Leu His Val Pro
        35                  40                  45

Asn Phe Leu Asn Tyr Ile Ser Arg Lys Asn Gln Ser Ser Leu Thr Asn
    50                  55                  60

Cys Phe Thr Ile Glu Leu Tyr Ile Ser Leu Ser Lys Ile Ile Asn Pro
65                  70                  75                  80

Arg His Val Thr Ile His Ile Lys Phe Cys Phe Ser Asp Lys Gly Ile
                85                  90                  95

Ile His His Asn Lys Leu Phe Val Phe Ile Ser Thr Gly Gln Ser Leu
            100                 105                 110

Glu Lys Val Arg Ser His Leu Tyr Phe Pro Val Pro Ser Asn Thr Phe
        115                 120                 125

Leu Leu Leu Phe Tyr Leu Ile Gln Cys Phe Ser Phe Leu Lys Thr Ile
    130                 135                 140

Gln Leu Lys Tyr Cys Thr Lys Asn Asn Phe Asn Ile Lys Tyr Leu Gln
145                 150                 155                 160

Phe Tyr Ser Ser Ser Cys Asp Lys Ile Gln Glu Asn Leu Thr Met Asn
                165                 170                 175
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ENSDOCID <WO 0166751A2_I_>

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Asn Asn Thr Thr Cys Ile Gln Pro Ser Met Ile Ser Ser Met Ala Leu
            180                 185                 190

Pro Ile Ile Tyr Ile Leu Leu Cys Ile Gly Gly Val Phe Gly Asn Thr
        195                 200                 205

Leu Ser Gln Trp Ile Phe Leu Thr Lys Ile Gly Lys Lys Thr Ser Thr
    210                 215                 220

His Ile Tyr Leu Ser
225
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<210> 212
<211> 154
<212> PRT
<213> Homo sapiens

<400> 212

```
Ser Pro Thr Leu Gln Phe Ser Lys Pro Trp Cys Thr Phe Asp Phe Leu
1               5                   10                  15

Leu Phe Gln Met Arg Ile Glu Met Trp Tyr Leu Gln Tyr Tyr Tyr Phe
            20                  25                  30

Cys Met Pro Ile Tyr Ala Pro Val Ser Ala Phe His Ala Leu Gly Ser
        35                  40                  45

His Arg Phe Val Val Ala His Glu Val Leu Glu Phe Leu Val Phe Asn
    50                  55                  60

Lys Lys Phe Leu Ser Ser Thr Glu Tyr Ile Thr Thr Ile His Ser Phe
65                  70                  75                  80

Tyr Phe Ile Leu Phe Glu Pro Asn Asn Ser Met Gln Lys Arg Lys Val
                85                  90                  95

Asp Ser Thr Val Gln Glu Pro Tyr Phe Arg Phe Glu Val Met Glu Leu
            100                 105                 110

Ser Gln Arg Ala Leu Val Leu Ile Arg Asp Gln Cys Thr Asp Gln Asn
        115                 120                 125

Thr Arg Cys Arg Leu Ile Phe Ser Phe Ser Gly Ser Ala Thr Leu Leu
    130                 135                 140

Arg Pro Thr Val Leu Phe Leu Cys His Val
145                 150
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<210> 213
<211> 154
<212> PRT
<213> Homo sapiens

<400> 213

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Val Cys Lys Trp Arg Phe Pro Tyr Leu Gln Val Ile Arg Lys Ile Lys
1               5                   10                  15

Tyr Ala Asn Leu Lys Thr Cys His Ser Met Asn Val Asn Phe Ser Leu
            20                  25                  30

Arg Cys Trp Trp Leu Gly Ala Leu Val Phe Ser Ile Phe Phe Tyr Cys
        35                  40                  45
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BNSDOCID <WO__ 0166751A2_I >

Phe Ser Pro Ser Thr Val Leu Leu Leu Ile Tyr Ser Phe Thr His Gln
50 55 60

Lys Ala Pro Lys Lys Ile Arg Val Gln Trp Met Asp Lys Pro Asp Phe
65 70 75 80

Leu Ser Thr Thr Leu Glu Cys Lys Val Ser Glu Asp Ser His Arg Lys
85 90 95

Tyr Asn Arg Ser Met Asn Ile Met Lys Arg Asn Tyr Arg Met Leu Lys
100 105 110

Leu Ile Asn Glu Asn Leu Ile Phe Trp Cys Ser Glu Asn Ile Phe Gln
115 120 125

Ile Val Ala Gly Arg Ile Ser Arg Cys Trp Gln Glu Arg Asp Pro Gly
130 135 140

Tyr Ser Arg His Met Lys His Arg Cys Arg
145 150

<210> 214
<211> 158
<212> PRT
<213> Homo sapiens

<400> 214

Lys Glu Ala Arg Thr Phe Thr Phe Leu His Thr Pro Ala Arg Met Phe
1 5 10 15

Arg Ile Ile Lys Gln Thr Lys Lys Ser Gln Val Gly Ile Tyr Phe Ala
20 25 30

Gly Glu Asp Gln Gly Arg Gly Gly Ser Gln Leu Pro Asn Val Val Gly
35 40 45

Gly Phe Leu Ile Gln Gln Leu Pro Gly Ala Asp Leu Ala Tyr Phe Trp
50 55 60

Ile Met Ala Glu Pro Gly Thr Glu Val Ser Ser Ile Ser Ser Arg Phe
65 70 75 80

Ile Ile Cys Gln Ile Pro Ala Ser Val Val Val Val Tyr Leu Leu Lys
85 90 95

Ala Lys Ala Glu Cys Phe Trp Glu Leu Leu Phe Val Pro Glu Tyr Glu
100 105 110

Asn Cys Ser Ser Ile Ser Ser Asn Lys Phe Val Gly Phe Glu Tyr Leu
115 120 125

Lys Phe Leu Val Ile Ile Ile Asn Tyr Gly Pro Ala Lys Ala Ser Ser
130 135 140

Leu Pro Val Phe Val Leu Thr Lys Trp Phe Leu His Phe Phe
145 150 155

<210> 215
<211> 203
<212> PRT
<213> Homo sapiens

<400> 215

```
Arg Met Gly Gln His Ser Lys Gln Glu Arg Ile Pro Lys Val His Asp
1               5                  10                  15

Phe Glu Ile Pro Leu Ile Lys Leu Thr His Leu Leu Pro His Leu Leu
            20                  25                  30

Val Trp Asn Leu Leu His Leu Phe Phe Ile Ala Ser Lys Phe Leu Phe
        35                  40                  45

Val His His Leu Ser Ser Leu Ile Arg Leu Leu Pro Pro Trp Arg Asn
    50                  55                  60

Val Tyr Ala Leu Lys Asn Phe Leu Gln Ala Gln Ser Cys Phe Ser Leu
65                  70                  75                  80

Lys Ala Cys Val Phe Lys His Ser Ser Thr Leu Trp Ser Thr Ser Asp
                85                  90                  95

Ile Leu Ala Val His Leu Pro Gly Ile Val Thr Asp Phe Gln Val Ala
            100                 105                 110

Ala Phe Ser Phe Ser Leu Met Cys Asn Phe Ser Lys Tyr Phe Thr Ile
        115                 120                 125

Glu Ile Ser Ser Arg Thr Gln Leu Trp Tyr Leu His Ser Lys Ser Thr
    130                 135                 140

Cys Phe Thr Asn Asn Lys Leu Asn Ile Ser Leu Cys Ser Ala Lys Thr
145                 150                 155                 160

Ala Tyr Tyr Ala Ile Ile Tyr Phe Thr Phe Ile Leu Leu Cys Thr Arg
                165                 170                 175

Lys Cys Ser Met Cys Phe Ala Leu Phe Ile Leu Phe Asn Pro His Lys
            180                 185                 190

Asn Tyr Ile Leu Thr Leu Ser Asp Leu Trp Gly
        195                 200
```

<210> 216
<211> 208
<212> PRT
<213> Homo sapiens

<400> 216

```
Lys Arg Tyr Glu Ile Asn His Thr Gly Asn Tyr Leu Thr Ser Asn Tyr
1               5                  10                  15

Lys Ala Val Asp Thr Phe Asn Ile His His Leu Phe Lys Cys Gln His
            20                  25                  30

Asn Ser Val Asp Cys Ile Ile Leu Met Val Phe Ile Met Pro Ile Ile
        35                  40                  45

Leu Ser Glu Asn Asn Asn Cys Ile Ile Cys Phe Phe Phe Thr Lys Glu
    50                  55                  60

Ile Ser Thr Gly Gly Met Ile Arg Asn Asn Lys Ile Asn Tyr Met Val
65                  70                  75                  80

Cys Glu Leu Lys Met Tyr Asn Leu Val Glu Arg Ile Cys Ala Leu Thr
                85                  90                  95
```


BNSDOCID: <WO__ 0166751A2_I_>

```
Arg Arg His Gly Asn Ile Phe Arg Leu His Phe Leu His Val Gln Asn
            100                 105                 110

Val Ser Ser Asn Asn Val Tyr Leu Thr Arg Tyr Leu Lys Ile Asn Val
        115                 120                 125

Pro Arg Gln Glu Val Gln Asp Leu His Ser Glu Ser Leu Ile Leu Ser
    130                 135                 140

Leu Val Phe Ser Pro Val Leu Cys Leu Thr Val Leu Phe Phe Met Phe
145                 150                 155                 160

Thr Ile Tyr Leu Ile Gly Lys Arg Asn Cys Ile His Gly Ile Phe Val
                165                 170                 175

Gly Leu Asn Lys Asp Lys Glu Pro Gly Ile Lys Leu Leu Ile Thr Leu
            180                 185                 190

His Val Gln Ile Ile Cys Ile Phe Ile Ile Val Asp Thr Leu Asn Tyr
        195                 200                 205
```

<210> 217
<211> 115
<212> PRT
<213> Homo sapiens

<400> 217

```
Asn Ser Met Val Leu Asn Lys His Thr Gln Leu Thr Tyr Leu Arg Glu
1               5                   10                  15

Tyr Ser Phe Tyr Ile Tyr Gln Ile Ile Arg Val Ile Cys Thr Asp Thr
            20                  25                  30

Ser Lys Ser Cys Leu Tyr Leu Gln Ser Pro Asn Ala Asn Tyr Leu Ser
        35                  40                  45

Leu Leu Asn Val Tyr Ser Val Leu Thr Thr Leu Leu Arg Ile Met Cys
    50                  55                  60

Glu Lys Asp Arg Leu Thr Ser Cys Cys Phe Asp Pro Arg Phe Lys Glu
65                  70                  75                  80

Arg Ser His Met Glu Leu Val Cys Ser Leu Tyr Asn Lys Leu Lys Ser
                85                  90                  95

Ile Leu Lys Ile Lys Ile Trp Val His Ser Ser Lys Thr His Lys Pro
            100                 105                 110

Ile Ser Thr
        115
```

<210> 218
<211> 205
<212> PRT
<213> Homo sapiens

<400> 218

```
Arg Met Lys Thr Val Cys Gln His Leu Phe Gly Tyr Ile His Gln Ile
1               5                   10                  15

Leu Asp Ser Val Lys Gly Gln Gln Arg Val Leu Met Leu Pro Pro Ala
            20                  25                  30
```


BNSDOCID <WO 0166751A2>

```
Pro Thr Arg Gly Asp Gly Asp Glu Leu Lys Pro Ser Tyr Phe Gly Arg
        35                  40                  45

Cys Ala Asp Ile Phe Thr Asn Gln Ser Tyr Gln Leu Val Ser Arg Val
    50                  55                  60

Ser Leu Ile Ile Ala Val Leu Leu Asn Ser Tyr Ile Tyr Thr Ile Met
65                  70                  75                  80

Phe Gly Glu Thr Lys Lys His Cys Trp Val Lys Ile Arg Val Phe Tyr
                85                  90                  95

Asn Leu Ile Cys Phe Thr Asp Glu Ala Ser Leu Gln Tyr Gly Pro Arg
            100                 105                 110

Thr Ser His Pro Val Met Gly Thr His Thr Ile Arg Ile Tyr Gln Ile
        115                 120                 125

Leu Tyr Val Gln Thr Cys Ile Thr Pro Cys Gly Tyr Leu Leu Arg Ser
    130                 135                 140

Ala Leu Leu Gly Asn Phe Val Thr Val Thr Trp Arg Ala Cys Thr Gln
145                 150                 155                 160

Thr Lys Ala Trp Ser Arg His Pro Thr Val Trp Arg Ser Pro Leu Leu
                165                 170                 175

Leu Gly Lys Pro Ala Gln His Val Thr Ile Leu Asn Thr Val Asp Ser
            180                 185                 190

Asn Thr Val Met Ser Ile Cys Val Tyr Lys Gln Ile Thr
        195                 200                 205

<210>  219
<211>  229
<212>  PRT
<213>  Homo sapiens

<400>  219

Ser Lys Met Arg Ile Trp Glu Met Ile Val Asn Gly Cys Lys Tyr Val
1               5                   10                  15

Gly Ser Trp Gly Pro Leu Gln Val Ser Leu Tyr Ser Leu Asn Thr Glu
            20                  25                  30

Ala Ser His Gln Cys Ser Gly Pro His Gln Ala Phe Cys Val His Ile
        35                  40                  45

His Glu Ala Ile Asn Gly Ala Ile Leu Pro Lys Ile Gln Leu Thr Pro
    50                  55                  60

Met Pro Ile Gln Leu Pro Asp Tyr Ser Arg Ser Arg Glu Pro Arg Gly
65                  70                  75                  80

Arg Val Gln Trp His His Arg Asp Gly Ala Gly Lys Ile Gln Asn Met
                85                  90                  95

Gly Asn Ser Gln Gln Thr Asp Pro Leu Phe Tyr His Val Asn Ser Gly
            100                 105                 110

Lys Thr Glu Arg Gln Gly Arg Val Met Trp Arg Glu Thr Glu Ala Cys
        115                 120                 125

Gln Leu Asn Ala Ile Asn Glu Pro Cys Phe Asp Cys Asp Ser Met Leu
```


BNSDOCID <WO 0166751A2_I_>

```
    130                 135                 140

Thr Glu Arg Lys Asn Thr Lys Leu Glu Phe Ile Leu Thr Arg His Leu
145                 150                 155                 160

Met Ile Leu Arg Asn Asp Cys Arg Phe Leu Gly Met Ile Met Val Leu
                165                 170                 175

Trp Leu Cys Phe Leu Lys Phe Leu Ile Trp Arg Thr Leu Ser Glu Arg
            180                 185                 190

Ala Ser Lys Lys Phe Gln Val Trp Glu Ser Val Leu Gly Glu Arg Lys
        195                 200                 205

Trp Thr Ser Ile Tyr Val Lys Asp Trp Thr Val Ile Lys Cys Gly Arg
    210                 215                 220

Thr Ala Gly Phe Lys
225

<210>  220
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  220

Glu Ala Leu Lys Met Ser Arg Arg Glu Gly Lys Lys Cys Phe Pro Trp
1               5                   10                  15

Val Trp Glu Ile Arg His Ser Asp Leu Ile Arg Gly Val Gly His Thr
            20                  25                  30

Ala Asn Gly Lys Lys Gln Gly Arg Asn Leu His Lys Ile Ser Phe Ile
        35                  40                  45

Phe Ala Leu Phe Lys Pro Leu Trp Ile Val Ile Leu Glu Thr Ala Thr
    50                  55                  60

Ile Phe Glu Ser Val Phe Cys Met Tyr Pro Phe Leu Asp Ser Cys His
65                  70                  75                  80

Asp Ser Ser Cys Leu Ser Met Ser Pro Val Leu Ser Lys Leu Cys Gln
                85                  90                  95

Val Ala His Ser Leu Pro His Ser Leu Asn Ala Ser Thr Arg Met Gln
            100                 105                 110

Thr Asp Asn Thr Val Ala Ala Ser Tyr Thr Cys Ser His Gln Ser Ala
        115                 120                 125

Asp Arg Cys Ser Leu Gly Val Ala Ala Gln Gln Phe Pro Gln Glu Ala
    130                 135                 140

Gly Leu Tyr Phe Phe Leu Leu Phe Leu Pro Trp His Val Tyr Leu Ser
145                 150                 155                 160

Ser Cys Leu Ser Pro His His Cys Lys Ile Ala Ala Ser Val Pro Ala
                165                 170                 175

Ile Thr Ser Thr Val Leu Pro Pro
            180

<210>  221
<211>  161
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BNSDOCID <WO 0166751A2_1_>

<212> PRT
<213> Homo sapiens

<400> 221

Trp Gly Pro His Gly Val Ile Thr His Trp Pro Thr Ser Ile Leu Leu
1 5 10 15

His Trp Tyr Leu Asn Phe Lys Ala Asp Phe Lys Gly Asn Thr Tyr Ser
20 25 30

Asn His Ser Lys Pro Ile Lys Ser Ile Leu Asn Phe His Phe Ser Ser
35 40 45

Phe Asp Phe Arg Ile Phe Phe Phe Phe Phe Leu Ile Gly Leu Leu Ser
50 55 60

Leu Leu Thr Leu Met Glu Lys Ile Phe His Ile Ser Glu Lys Thr Ser
65 70 75 80

Phe Pro Leu Asp Leu Leu Ile His Ala Gln Ser Phe Ile Ser Phe Leu
85 90 95

Ile Asn Thr Arg Ser Val Phe Phe Tyr Ser Asp Leu Asp Asp Cys Leu
100 105 110

Ser Ile Gln Asn Ala Phe Leu Phe Tyr Phe Phe Phe Cys Leu Pro Leu
115 120 125

Val Cys Leu Val Ile Phe Cys Cys Gln Leu Asp Met Leu Tyr Gln Val
130 135 140

Ile Arg Ile Val Val Asn Arg Ser Leu Val Gly Leu Ile Cys Ser Gly
145 150 155 160

Val

<210> 222
<211> 210
<212> PRT
<213> Homo sapiens

<400> 222

Phe Phe Cys Asn Glu Phe Glu His Cys Arg Ser Phe Ile Asn Val Ile
1 5 10 15

Phe Lys Phe Tyr Met Cys Cys Arg Ser Glu His Lys Leu Met Ser Phe
20 25 30

Ser Ser Thr Ala Ile Pro Gln Tyr Ser Gln Gly Thr Gly Ser Arg Thr
35 40 45

Pro Val Asn Thr Lys Thr Gln Gly Cys Ser Ser Leu Leu Tyr Thr Met
50 55 60

Val Tyr Leu His Ile Thr Cys Ser Arg Pro Ser Val Tyr Phe Lys Ser
65 70 75 80

Ser Leu Asp Tyr Leu Tyr Leu Ile Cys Lys Cys Tyr Val Asn Ser Cys
85 90 95

Thr Val Leu Leu Lys Phe Glu Phe Phe Asn Val Ile Leu Lys Phe Phe
100 105 110

BNSDOCID <WO___0166751A2_I_>

Ser Glu Tyr Phe Gln Ser Ala Val Gly Ile Gln Pro Met Asp Thr Glu
115 120 125

Arg Val Tyr Asn Leu Thr His Leu Ile Leu Ser Thr Phe Cys Gln Cys
130 135 140

Phe Arg Phe Leu Leu Trp Tyr Phe Lys Asn Ser Ile Phe Leu Pro Leu
145 150 155 160

Leu Phe Trp Val Pro Gln Gly Lys Asp Tyr Leu Val His Leu Cys Ile
165 170 175

Phe Asn Ser Trp Tyr Ser Val Trp Asn Thr Val Gly Glu Leu Ser Lys
180 185 190

Trp Gly Tyr Pro Lys Ser Gly Glu Asn Leu Leu Asp Asp Leu Asp Asp
195 200 205

Leu Leu
210

<210> 223
<211> 178
<212> PRT
<213> Homo sapiens

<400> 223

Arg Leu Ser Phe Thr Gly Pro Phe Ser Asp Pro Ser His Ala Lys Leu
1 5 10 15

Ile Leu Ser Thr Gly Leu Cys Ile Cys Ser Phe Leu Cys Trp Thr Pro
20 25 30

Phe Phe Leu Ala Cys Leu Ile Cys Ile Tyr Leu Lys Asp Leu Ala Tyr
35 40 45

Val Phe Leu Ser Gln Glu Ser Phe Pro Pro Ser Ile Cys Leu Lys Val
50 55 60

Asp Ile Pro Ser Glu Ile Ile Asn Ser Asn Asp Gly Asn Asn Asn Asn
65 70 75 80

Ser Ser Asn Leu Val Phe Met Ser Cys Arg Asp Cys Ser His Leu His
85 90 95

Ile Gly Ser Phe Leu Val Phe Ile Ala Thr Leu Val Val Val Gly Lys
100 105 110

Val Gly Pro Arg Ile Ile Cys Ile Leu Met Arg Lys Leu Lys Gly Met
115 120 125

Leu Ser His Leu Ser Lys Val Thr Gln Pro Phe Gly Ser Arg Val Gly
130 135 140

Ile Thr Arg Ala Asp Pro Ser Ala His Val Leu Asn Cys Cys Ala Leu
145 150 155 160

Leu Trp Val Leu Cys Asn Val Phe Cys Cys Leu Pro Leu Leu Glu Ala
165 170 175

Leu Ser

ENSDOCID <WO 0166751A1 >

<210> 224
<211> 113
<212> PRT
<213> Homo sapiens

<400> 224

Leu Leu Phe Ile Ile Ile Leu Lys Ser Gln Val Lys Leu Trp Phe Thr
1 5 10 15

Ile Tyr Gln Glu Gln Asn Val Ser Ile Lys Thr Leu Glu Gly Ile Lys
20 25 30

Tyr Asn Gly Asn Ser Leu Ile Met Ser Cys Phe Asn Glu Asn Glu Leu
35 40 45

Val Leu Lys Ser Phe Lys His Lys Gly Lys Cys Val Thr Asn Met Lys
50 55 60

Ser Cys Met Phe Ile Cys Phe Thr Met Val Gln Phe Leu Leu Cys Ile
65 70 75 80

Cys Ile Pro His His Phe Val Cys Leu Gln Tyr Thr Lys Asn Leu Phe
85 90 95

Lys Met Asn Ile Ala Leu Met Arg Lys Asp Leu His Lys Ile Ser Gln
100 105 110

Tyr

<210> 225
<211> 72
<212> PRT
<213> Homo sapiens

<400> 225

Val Gly Lys Lys Lys Thr Val Leu Phe Leu Pro Phe His His Ala Val
1 5 10 15

Ser Lys Cys Thr Val Asp Leu Gly Val Phe Ser Ser Leu Asp Lys Leu
20 25 30

Leu Cys Asn Cys Thr Ser Leu Ile Leu Phe Tyr Phe Tyr Lys Gln Asn
35 40 45

Ile Met Tyr Ser Val Leu Thr Leu His Asp His Met Gln Ser Cys Leu
50 55 60

Gln Val Cys Phe Gln His Trp Leu
65 70

<210> 226
<211> 201
<212> PRT
<213> Homo sapiens

<400> 226

Gly Trp Pro Leu Phe Tyr Thr Val Tyr Leu Tyr Phe Ala Cys Ser Ser
1 5 10 15

Leu Phe Leu Phe Ser Ser Phe Ile Pro Ser Leu Ala Ala Ile Asn Leu
20 25 30

BNSDOCID <WO__ 0166751A2_I_>

```
Pro Val Ile Pro Ser Ser Phe Leu Pro Val Thr Thr Asn His Phe Pro
        35                  40                  45

Leu Arg Ser Pro Glu Leu Asn His His Ser Ser His Phe Gln Phe Asn
    50                  55                  60

Ser Thr Phe Phe Lys Thr Tyr Ser Asp Leu Ile Val Cys Leu His Leu
65                  70                  75                  80

Cys Gly Ile Thr Ser Ile Ser Asn Leu Asp Tyr His Asn Ser Leu Gln
                85                  90                  95

Thr Asp Phe Ala Val Ser Lys Thr Phe Ala Ser Leu Leu Tyr Ile Phe
            100                 105                 110

Cys Pro Gly Ala Val Ile Thr Phe Lys Tyr Lys Ser Tyr Gln Val Thr
        115                 120                 125

Ser Leu Leu Lys Thr Leu Gln Trp Ser Gln Thr Lys Ile Ser Lys Val
    130                 135                 140

Leu Lys Thr Ala Tyr Ile Ile Ile Phe Leu Phe Gln Leu Ile Ser Gln
145                 150                 155                 160

Ser Phe Ser Phe Asp Thr Ile Ala Phe Ser Leu His Pro Cys Asn Tyr
                165                 170                 175

Pro Ser Lys Ser Ile Ser Pro Thr Asn His Phe Gln Thr Ile Leu Phe
            180                 185                 190

Phe Asn Ile Ile Tyr His Tyr Gln Ile
        195                 200

<210>  227
<211>  160
<212>  PRT
<213>  Homo sapiens

<400>  227

Gly Trp Lys Ser Pro Leu Val Arg Ala Glu Pro Lys Lys Thr Lys Ala
1               5                   10                  15

Val Tyr Tyr Asn Pro Ile Leu Pro His Phe Ala Glu Lys Pro Thr Leu
            20                  25                  30

His Ile Cys Val Asn Val Arg Ala Ala Lys His Pro Cys Ile Leu Arg
        35                  40                  45

Arg Cys Gly Leu Thr Arg Val Thr Ala Ser Ala Asp Thr Ile Gly Tyr
    50                  55                  60

Leu Val Leu Cys Trp Phe Ala Gly Phe Phe Phe Asn Ser Leu Asn Ser
65                  70                  75                  80

Ile Leu Pro Thr Met Cys Ser Pro Pro Leu Leu Thr Gly Ile Phe Leu
                85                  90                  95

Ile Ala His Leu Cys Leu Phe Leu Gly Lys Phe Gly Pro Met Gln Ser
            100                 105                 110

Thr Val Cys Thr Ala Leu Val Asn Val Ser Val Ala Leu Ser Ser Gln
        115                 120                 125
```


ENSDOCID <WO 0166751A2_I>

Leu Pro Phe Glu Gln Gln Ser Gln Met Glu Ser Asp His Ser Leu Val
130 135 140

Tyr Gly Lys Asp Gly Leu Phe Ser Ser Ala Leu Ser Lys Gln Lys Gln
145 150 155 160

<210> 228
<211> 196
<212> PRT
<213> Homo sapiens

<400> 228

Ile Ile Met Ser Arg Ile Ile Ala Ser Ile Lys Glu Asn Glu His Tyr
1 5 10 15

Thr Gln Ser Lys His His Leu Glu Asn Val Gln Met Ile Ala Ala Gln
20 25 30

Phe Ile Ile Ile Ile Ile Ala Leu Lys Lys Lys Glu Glu Lys His Thr
35 40 45

Trp Ala Lys Leu Cys Lys Leu Ile Ser Ala Thr Cys Glu Leu Cys Asp
50 55 60

Phe Gly Phe Ile Ile Phe Glu Gly Phe Phe Phe Leu Cys Leu Asn Gly
65 70 75 80

Val Ser Phe Thr Tyr Leu Gln Val Ile Arg Lys Ile Lys Tyr Ala Asn
85 90 95

Leu Lys Thr Cys His Ser Met Asn Val Asn Phe Ser Leu Arg Cys Trp
100 105 110

Trp Leu Gly Ala Leu Val Phe Ser Ile Phe Phe Tyr Cys Phe Ser Pro
115 120 125

Ser Thr Val Leu Leu Leu Ile Tyr Ser Phe Thr His Gln Lys Ala Pro
130 135 140

Lys Lys Ile Arg Val Gln Trp Met Asp Lys Pro Asp Phe Leu Ser Thr
145 150 155 160

Thr Leu Glu Cys Lys Val Ser Glu Asp Ser His Arg Lys Tyr Asn Arg
165 170 175

Ser Met Asn Ile Met Lys Arg Asn Tyr Arg Met Leu Lys Leu Ile Asn
180 185 190

Glu Asn Leu Ile
195

<210> 229
<211> 156
<212> PRT
<213> Homo sapiens

<400> 229

Leu Glu Arg Glu Leu Ser Pro Asp Ser Val Leu Trp Val Leu Phe Ala
1 5 10 15

Thr Cys His Val Ile Arg Asp Ile Ile Ala Asn Cys Gln Leu Phe Cys
20 25 30

ENSDOCID <WO 0166751A2_I_>

```
Asn His Thr Thr Leu Phe Leu Leu Ser Pro Val Ser Ile Thr Leu Phe
        35                  40                  45

Ala Phe Trp Ser Leu Thr Gly Phe Phe Ser Pro Gln Val Gln Val Phe
    50                  55                  60

Gln Asn Ile Thr Phe Thr Leu Phe Leu Leu Pro Phe Gln Pro Gln Ser
65                  70                  75                  80

Ala Ile Trp Tyr Gln Ser Gln Cys Pro Leu Tyr Leu Asp Leu Met Ser
                85                  90                  95

Cys Thr Leu Leu Leu Gly Ile Asn Phe Cys Ile Ser Tyr Val Leu Leu
            100                 105                 110

Asp Asn Lys Leu Pro Gln Met Glu Leu His Ile Ile Ile Ile Asp Ile
        115                 120                 125

Tyr Val Ser Asn Asn Phe Phe Leu Asn Gln Phe Ser Leu Glu His Leu
    130                 135                 140

Arg Gln Gln Arg Ser Val Glu Cys Asp Cys Val Gly
145                 150                 155

<210>  230
<211>  169
<212>  PRT
<213>  Homo sapiens

<400>  230

Phe Thr Leu Val Leu Ile His Phe Cys Ser Leu Phe Lys Ile Ala Ile
1               5                   10                  15

Leu Lys Phe Phe Val Val Cys Trp Ala Ala Leu Asp Thr Val Phe Ser
            20                  25                  30

Thr Cys Phe Phe Phe Ser Phe Glu Ala Ile Phe Ser His Leu Ser Asp
        35                  40                  45

Leu Phe Cys Cys Cys Cys Lys Leu Asp Ile Leu Leu Cys Asp Lys Ser
    50                  55                  60

Gly Asn Gln Ile Leu Ser Leu Pro Gln His Phe Phe Leu Ile Ser Glu
65                  70                  75                  80

Asp Cys Ser Asn Val Cys Phe Tyr Thr Phe Pro Ser Tyr Phe Cys Lys
                85                  90                  95

Asp Tyr Ser Leu Phe Phe Cys Gly His Gln Ser Val Cys Phe Phe Ser
            100                 105                 110

Leu Cys Leu Ala Ser Val Leu Thr Glu Ile Ser Leu Asn Ala Arg Ser
        115                 120                 125

Lys Thr Thr Pro Thr His Thr His Thr His Thr His Thr His Thr His
    130                 135                 140

Thr Tyr Thr His Lys His Thr Ser Pro Ile Phe Cys Lys Leu Gly Leu
145                 150                 155                 160

Gly Leu Phe His Leu Cys Asp Lys Ser
                165

<210>  231
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BNSDOCID <WO 0166751A2_I_>

<211> 117
<212> PRT
<213> Homo sapiens

<400> 231

Ala Ser Arg Ala Ser Val Gly Val Arg Gly Pro Ser Leu Arg Gly Val
1 5 10 15

Pro Ala Arg Gln Arg Ser Arg Val Ser Arg Ser Gly Arg Gly Ser Gly
20 25 30

Thr Gly Gly Ala Pro Arg Pro Ser Leu Ala Ala Ala Gln Arg Pro Val
35 40 45

Gln Ala Ser Ser Trp Ala Gly Arg Arg Gly Thr Gly Glu Leu Lys Pro
50 55 60

Arg Gly Arg Lys Pro Glu Pro Val Ala Ala Ala Gly Val Gly Arg Gly
65 70 75 80

Val Gly Arg Leu Leu Gly Gln Arg His Thr Ala Ala Gln Trp Met Leu
85 90 95

Thr Ala Ala Gly His Pro Asp Leu Tyr Gly Arg Leu Cys Ser Phe Leu
100 105 110

Leu Pro Glu Val Gly
115

<210> 232
<211> 193
<212> PRT
<213> Homo sapiens

<400> 232

Asn Ile Ser Cys Ile Cys Gly Ala Val Glu Thr Gln Pro Tyr Ser Phe
1 5 10 15

Leu Pro Asn Phe Pro Phe Asn Leu Phe Gly Gln Phe Phe Met His Ser
20 25 30

Trp Leu Ser His Met Gly Ser Ile Val Val Cys Val Thr Tyr Lys Ile
35 40 45

Glu Asn Pro Asp Pro Ser Asn Asn Ile Phe Phe Lys Ser Ile Ala Gly
50 55 60

Cys Ala Cys Ile Cys Ile Pro Tyr Thr Ser Thr Pro Phe Met Ser Leu
65 70 75 80

Thr Ala Leu Cys Gly Arg Lys Lys Pro Arg Asp Arg Gly Ser Ser Leu
85 90 95

Cys Ser Ala Pro Cys Pro Met Val Tyr Lys Gly Asn Gly Arg His Met
100 105 110

Ala Ser Leu Gly Leu Ser Phe His Thr Cys Lys Met Arg Met Thr Pro
115 120 125

Arg His Thr Leu Gln Gly Ser Gln Lys Glu Ile Trp Cys Leu Gln Arg
130 135 140

Tyr Leu Ala His Ala Glu Lys Gly Pro His Glu Cys Pro Ser Phe Leu

ENSDOCID <WO 0166751A2 I>

145 150 155 160

Ile Tyr Glu Arg Glu Glu Glu Tyr Trp Pro Val Cys Glu Ser Ile Gln
165 170 175

Ala Ser Thr Thr Ser Pro Ala Phe Ser Ala Lys Asn Thr Leu Arg Ile
180 185 190

Leu

<210> 233
<211> 185
<212> PRT
<213> Homo sapiens

<400> 233

Leu Cys Gly Ser Gln Pro Trp Asp Val Ser Leu Ser Glu Ser Gln Ile
1 5 10 15

Gly Asn Ile Pro Met Ile Lys Gly Phe Arg Trp Asn Gln Thr Val Gly
20 25 30

Glu Ser His Phe Gln Lys Ile Asn Trp Thr Ser Ser Glu Leu Lys Ser
35 40 45

Cys Val Gln Gly Gly Glu Arg Ile Gly Glu Ala Ser Phe Pro Ile Leu
50 55 60

Leu Leu Lys Lys His Met Gly Val Ser Ser Val Leu Val Leu Lys Arg
65 70 75 80

Ala Pro His Leu Glu Phe Asn Ala His Gly His Cys Pro Ala Thr Phe
85 90 95

Ser Ser Cys Leu Ile Arg Ile Leu Val Lys Ser Asp Gly Thr Arg Lys
100 105 110

Thr Trp Lys Leu Glu Ala Ser Ser Pro Ser Trp Ser His Leu Leu Leu
115 120 125

Pro Ser Cys Leu Pro Gly Met Val Pro Trp Leu Ser Leu Ser Pro Pro
130 135 140

Ser Asp His Cys His Leu Leu Thr Leu Ala Gly Ala Trp Ala Gln Lys
145 150 155 160

Gln Gly Gly Leu Gly Phe Trp Arg His Gly Pro Gly Ile Cys Arg Gly
165 170 175

Phe Thr His Phe Met Ser Ile Pro Met
180 185

<210> 234
<211> 212
<212> PRT
<213> Homo sapiens

<400> 234

Thr Trp Tyr Arg Leu Asn Thr Ser Gln Arg Ser Pro Ala Ile Val His
1 5 10 15

Phe Arg Val Phe Leu Ser Trp Asn His Leu Ile Ile Ser Gly Lys Val

ENSDOCID <WO 0166751A2 I>

20 25 30

Ala Asn Leu Ile Ile Gln Lys Phe Lys Met Ser Ile Ile Tyr Pro Val
35 40 45

Pro Phe Leu Lys Ile Met Ile Thr Gln Glu Val Gly Ile Ser Gly Lys
50 55 60

Glu His Cys Asp Val Trp Leu Glu Gln Glu Met Cys Ile Ser Cys Ser
65 70 75 80

Val Leu Ser Phe Gly Ser Asn Arg Asp Trp Leu Ile Ile Gly Thr Gln
85 90 95

Ile Ser Val Glu Ile Thr Gln Glu Glu Val Trp Gly Asp Gln Gln Leu
100 105 110

Val Ile Asn Cys Leu Ser Ser Met Trp Glu Ser Ala Gly Pro Gly Asp
115 120 125

Ser Trp Ile Ser Gly Ser Leu Phe Ile Pro Gly Gly Ser Ser Trp Gly
130 135 140

Pro Ser His Ser Ala Met Gly Ser Cys Phe Ser Leu Tyr Glu Val Thr
145 150 155 160

Phe Leu Cys Thr Gln Arg Tyr Leu Ser Thr Ile Arg Ser Val Leu Arg
165 170 175

Gln Arg Val Arg Ala Trp Thr Lys Ile Lys Met Asn Ile Cys Asp Tyr
180 185 190

Ala His Thr Trp Tyr Arg His Val His Ile Cys His Arg His Lys Tyr
195 200 205

Met Glu Ile Glu
210

<210> 235
<211> 205
<212> PRT
<213> Homo sapiens

<400> 235

Leu Cys His Leu Gly Pro Gln Leu Val Phe Ile Val Gln Trp Ala Ala
1 5 10 15

Ser Glu Ser Pro Gly Cys Asp Pro Gly Asp Leu Pro Ser Leu Lys Pro
20 25 30

Leu Ala Phe Pro Thr Pro Gln Gly Pro Leu Trp Gln Pro Ala Arg Cys
35 40 45

Ala Val Leu Pro Met Val Gly Thr Val Val Cys Ala Ser Leu Leu Leu
50 55 60

Ile Arg Asn Phe Arg Ile His Val Phe Cys Leu Leu Val Cys Cys Ile
65 70 75 80

Ser Arg Lys Thr Val Trp Cys Pro Trp Val Leu Leu Ala Thr Ser Pro
85 90 95

His Arg Asn Thr Thr Ile Thr Thr Asn Ala Ser Leu Asn Thr Ile Phe
100 105 110

BNSDOCID <WO__0166751A2_I_>

```
His Tyr Ser Lys His Phe Ile Cys Ile Asn Tyr Gln Leu His Leu Leu
        115                 120                 125

Leu Gly Lys Cys Tyr His Ile Leu Phe Leu Gln Ile Met Arg Gln Thr
    130                 135                 140

Glu Arg Leu Cys Asp Ser Leu Gly Ala Ala Gln Leu Val Ser Asp Gly
145                 150                 155                 160

Pro Arg Ala Pro Ser Arg Asp Thr Val Leu Asn His Arg Ala Val Leu
                165                 170                 175

Pro Pro Thr Glu Leu Gly Ala Pro Arg Gly Gly Gly Gly Glu Arg Arg
            180                 185                 190

Asn Val Arg Arg Gly Glu Met Gly Ile Trp Arg His Lys
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Glu Val Ile Leu Trp Phe Ser Cys Trp Ile Val Ile Leu Lys Ser Pro
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Arg Pro Leu Thr Cys Leu Met Ser Trp Lys Asp Gly Lys Leu Gly Ser
        35                  40                  45

Ala Gly Thr Thr Arg Ser Asn Tyr Leu Trp Pro Leu Tyr His Ser Gly
    50                  55                  60

Leu Arg Ile Ile Lys Leu Ile Thr Trp Gln Leu Thr Ser Pro Gly Val
65                  70                  75                  80

Asn Val Ala Glu Pro Gly Arg Gly Phe Met Ala Phe Thr Asp Phe Val
                85                  90                  95

Ser Lys Leu Lys Gln Gln His Phe His Phe Ile Gln Ser Leu Thr Ser
            100                 105                 110

Arg Ser Ser Arg Gln His Lys Phe Lys Glu Arg Ala Ile Arg Leu His
        115                 120                 125

Leu Leu Met Gln His Gly Arg Val Lys Ser Met Trp Asp Gly Ser Tyr
    130                 135                 140

Trp Gly His Pro Trp Glu Lys Gln Ala Ala Thr Leu His Ile Leu Lys
145                 150                 155                 160

Leu Val Ile Phe Ala Cys Trp Leu Pro Tyr Tyr Ile Leu Leu Lys Ala
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Leu Ile Asp Ser Ile Phe Leu Met Ser Leu Ser Glu Thr
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Cys Gly Phe Cys Leu Ile Val Ser Cys Val His Arg Glu Pro Val Phe
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Ser Gln Leu Cys Lys Ser Trp Leu Phe Phe Ser Pro Thr Ile Val Trp
35 40 45

Ala Leu Ser Glu Gly Glu Ile Trp Ser Tyr Ser Gly Val Thr Arg Gly
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Arg Ile Leu Met Ala Pro Leu Val Ser Thr Ala Val Leu Asn Ala Leu
65 70 75 80

Leu Asn Lys Pro Gly Asp Phe Leu Cys Thr Val Leu Arg Leu His Pro
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Leu Arg Leu Ala Leu Tyr Lys Asp Ala Lys Arg Gln Thr Leu Pro Arg
100 105 110

Tyr Leu Cys Ala Pro Ser Pro Ile Asp Gly Glu Gln Lys Arg Tyr Glu
115 120 125

Ser Phe Thr Glu Ala Asp Ile Thr Cys Arg Leu Trp Pro Gln Val Phe
130 135 140

Val Thr Cys Gln Gly Gln Lys Lys Tyr Arg Gln Leu Glu Ser Phe Cys
145 150 155 160

Glu Tyr Lys Glu Glu Lys Lys Ile Ser Gln Ser Cys Lys Met Leu Tyr
165 170 175

Val Val Ser Ser Leu Phe Ser Ser Leu Lys Val Asn Tyr Arg Thr His
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Phe His Arg Glu Leu Phe Ser
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Asn Arg Leu Asn Pro His Cys Glu Phe His Thr Cys Val Asp Val Ser
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Thr Ser Arg Asp Gly Cys Ile Phe Phe Ile Phe Leu His Thr Phe Leu
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ENSDOCID <WO 0166751A2 I

Glu Tyr Phe Ile Ser Met Val Leu Gln Ile Leu Leu Pro Thr Tyr Cys
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Gly Phe Lys Ala Met Glu Lys Thr Lys Ser His Arg Ser Lys Tyr Cys
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Arg Lys Gln Asn Ser Trp Val Asp Leu Ile Phe Leu Tyr Lys Asn Tyr
100 105 110

Gly Tyr Gly Tyr Met Tyr Leu Cys Met Ser Val Ala Lys Ile Asn Lys
115 120 125

Met Asn Thr Phe Asn Leu Arg Val Pro Ile Ile Gln Phe Thr Ser Phe
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Cys Pro Thr Thr Leu Glu Ala Lys Thr Leu Val Glu Thr Leu Met Cys
145 150 155 160

Phe Thr Ser Asn Ser Ser Leu Ala Leu Asn Ile Pro Leu Phe Val His
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Pro Leu Ser Asp Ala Ile Leu Leu Val Lys Gln Gln Thr Ser Thr His
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Arg Lys Leu Glu Val Met Met Pro Ser Phe
195 200

<210> 239
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<212> PRT
<213> Homo sapiens

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Thr Ile Gly Val Arg Arg Ser Asp Phe Ile Phe Tyr Leu Glu Val Ile
35 40 45

Ser Cys Asn His Pro Lys Leu Ala Trp Tyr Leu Ser Phe Leu Asp Ala
50 55 60

Ser Phe Ser Phe Met Gln Trp Ser Ala Ser Phe Tyr Phe Leu Pro Pro
65 70 75 80

Ser Tyr Gly Val Val Phe Lys Met Asn Leu Cys Ser Ser Val Val Ser
85 90 95

Leu Val Pro Trp Phe Ser Leu Lys Ala Trp Ser Leu Asp Gln Gln His
100 105 110

Gln His His Leu Lys Val Cys Lys Cys Lys Phe Ser Ser Gln Pro Lys
115 120 125

Thr Tyr Thr Arg Asn Ser Arg Gly Arg Val Gln Ser Val Leu Thr Ser
130 135 140

Pro Pro Gly Gly Phe Gln Cys Met Leu Asn Leu Lys Ala Thr Leu Leu
145 150 155 160

Gly Gln Met Ile Leu Leu Ile Asn Ser Tyr His Tyr Ala Gly Pro Glu

ENSDOCID <WO 0166751A2 I>

165 170 175

Thr Lys Ser Asn Ser Val Lys Tyr Leu Ile Asn Lys Gln Leu Ile Phe
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Lys Leu Phe Leu Gln Ala Ala Leu Ile Thr Gly Ile His Gly Ser Gln
195 200 205

Val

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<400> 240

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20 25 30

Lys Val Leu Tyr Ala Thr Asn Thr Thr Ala Ile Ser Thr Gly Lys Ser
35 40 45

Leu Ser Leu Gln Lys Pro Ile Gln Lys Pro Arg Arg Ser Asn Cys His
50 55 60

Thr Lys Tyr Thr Asp Thr Asn Leu Arg Thr Glu Thr Glu Asn Lys Glu
65 70 75 80

Thr Trp His Phe Arg Ser Thr Ile Thr Leu Lys Lys Ile Gln Lys Thr
85 90 95

Phe Ile Lys Cys Leu Lys Glu Ile Gln Asn Asn Asn Ile Lys Glu Thr
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Gln Asp Ile Arg Glu Asn Arg Thr Thr Gln Arg Asn Lys Glu Asn Lys
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Ser Gly Phe Glu Glu Ile Pro Gln Arg Asp Arg Cys Lys Glu Thr Lys
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<220>
<223> Novel Sequence

<400> 241

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BNSDOCID <WO 0166751A2_I>

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(10) International Publication Number
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60/187,708	8 March 2000 (08.03.2000)	US
60/188,290	8 March 2000 (08.03.2000)	US
60/188,292	8 March 2000 (08.03.2000)	US
60/187,827	8 March 2000 (08.03.2000)	US
60/188,293	8 March 2000 (08.03.2000)	US
60/187,639	8 March 2000 (08.03.2000)	US
60/187,583	8 March 2000 (08.03.2000)	US
60/187,709	8 March 2000 (08.03.2000)	US
60/187,637	8 March 2000 (08.03.2000)	US
60/187,640	8 March 2000 (08.03.2000)	US

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(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **VOGELI, Gabriel** [US/US]; 2576 9th Avenue West, Seattle, WA 98119 (US).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
28 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The present invention provides a gene encoding a G protein-coupled receptor termed nGPCR-x; constructs and recombinant host cells incorporating the genes; the nGPCR-x polypeptides encoded by the gene; antibodies to the nGPCR-x polypeptides; and methods of making and using all of the foregoing.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/07370

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705 C12N15/11 C07K16/28 A61K39/00
G01N33/68 C12Q1/68 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, SEQUENCE SEARCH, CHEM ABS Data, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] ID: HSJ117L23; Accession number: AL049824, 23 November 1999 (1999-11-23) "Human DNA sequence from clone 117L23 on chrmosome 1p33-34.2" XP002177912 abstract ---	1,5,22, 25,67, 69,70
X	DATABASE EMBL [Online] ID: AQ227654; Accession number AQ227654, 4 March 2000 (2000-03-04) XP002177913 abstract --- -/--	1,5,22, 23,25, 69,70

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2001	15.01.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Macchia, G

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Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO__0166751A3_I_>

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 01/07370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE EMBL [Online] ID: AQ040412; Accession number AQ040412, 4 March 2000 (2000-03-04) XP002177914 abstract	1,5,22, 23,25, 69,70

X	WO 99 58641 A (MILLENNIUM PHARM, INC (US); CURTIS RORY; GLUCKSMANN MARIA ALEXANDRA) 18 November 1999 (1999-11-18) abstract page 48 -page 67 page 85 -page 86 figures 2,3	40,42, 43,45, 46,48, 74-77

A	WO 99 37679 A (MILLENNIUM PHARM INC (US); GLUCKSMANN M. ALEXANDRA; ROBISON KEITH) 29 July 1999 (1999-07-29) abstract	

A	WO 99 05274 A (SMITHKLINE BEECHAM CORP (US) SMITHKLINE BEECHAM PLC (GB) BERGSMA WILSO) 4 February 1999 (1999-02-04) the whole document	

A	PROBST W.C. ET AL.: "Sequence alignment of the G-protein coupled receptor superfamily" DNA AND CELL BIOLOGY, vol. 11, no. 1, 1992, pages 1-20, XP002920805 ISSN: 1044-5498 page 3 -page 9; figure 2	

A	LEE N.H. AND KERLAVAGE A.R.: "Molecular biology of G-protein-coupled receptors" DRUG NEWS AND PERSPECTIVES, vol. 6, no. 7, 1 September 1993 (1993-09-01), pages 488-497, XP000677175 ISSN: 0214-0934 page 491; figure 3	

A	EDVARDSEN O. AND KRISTIANSEN K.: "Internet resources on G-protein-coupled receptors" TIBS TRENDS IN BIOCHEMICAL SCIENCES, vol. 22, no. 6, 1 June 1997 (1997-06-01), pages 226-227, XP004074685 ISSN: 0968-0004 the whole document	

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

ENSDOCID <WO 0166751A3 | >

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 01/07370

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 39 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 44, 47, 52 all in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-81 all partially.

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

ENSDOCID <WO___0166751A3_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 44, 47, 52 all in part

Present claim 44 relates to a compound defined by reference to a desirable characteristic or property, namely its capability of binding to the polypeptide(s) disclosed in present application.

Present claim 47 relates to a compound defined by reference to a desirable characteristic or property, namely its capability of binding to the nucleic acid molecule(s) encoding the polypeptide(s) disclosed in present application.

Present claim 52 relates to a compound defined by reference to a desirable characteristic or property, namely its capability of modulating the activity of the polypeptide(s) disclosed in present application.

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In fact, concerning the subject-matter of claim 44, only antibodies binding to the polypeptide(s) of present application are mentioned (see pages 36-38).
Analogously, concerning the subject-matter of claim 47, only antisense molecules hybridizing to the nucleic acid molecule(s) encoding the polypeptide(s) of present application are mentioned (see pages 27-28).
Moreover, concerning the subject-matter of claim 52, on page 49 present application recites that " selective modulators may include, for example, antibodies and other proteins, peptides or organic molecules that specifically bind to a nGPCR-x (i.e. one of the polypeptides of present applictation) or a n-GPCR-x-encoding nucleic acid ".

However, no specific peptides, organic molecules, or proteins other than antibodies are disclosed or defined in present application as having one of said specific characteristics or properties.

Therefore, in the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define a compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies (for the subject-matter of claims 44 and 52) and antisense molecules (for the subject-matter of claims 47 and 52), as defined on pages 27, 28, 36-38 and 49 of present application.

BNSDOCID <WO__0166751A3_I>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

BNSDOCID <WO... 0166751A3_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-81 all partially

Nucleic acid molecule comprising a nucleotide sequence as in SEQ ID NO:1.
Related nucleic acid molecules and compositions therof, vectors and compositions thereof, host cell transformed with said vectors, methods and kits.
Polypeptide comprising an amino acid sequence as in SEQ ID NO:121.
Related polypeptides and compositions thereof, antibodies and compositions thereof and methods.

2. Claims: 1-81 all partially

Inventions 2-120

Idem as subject 1 but limited to each of the DNA sequences as in SEQ ID NO:2-120 and each of the polypeptides as in SEQ ID NO: 122-240, where invention 2 is limited to SEQ ID NO:2 and 122, invention 3 is limited to SEQ ID NO:3 and 123, ..., invention 120 is limited to SEQ ID NO:120 and 240).

For the sake of conciseness, the first subject matter is explicitly defined, the other subject matters are defined by analogy thereto.

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Inter .nal Application No
PCT/US 01/07370

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9958641	A	18-11-1999	AU	3897699 A	29-11-1999
			EP	1078040 A1	28-02-2001
			WO	9958641 A2	18-11-1999
WO 9937679	A	29-07-1999	US	5945307 A	31-08-1999
			AU	2236999 A	09-08-1999
			EP	1056777 A1	06-12-2000
			WO	9937679 A1	29-07-1999
WO 9905274	A	04-02-1999	WO	9905274 A1	04-02-1999

BNSDOCID <WO___0166751A3_I_>